131. (New) The osteoimplant of Claim 127 possessing a total thickness of from about 2 to about 20 mm.

132. (New) The osteoimplant of Claim 125 configured and dimensioned as a square or rectangle.

133. (New) The osteoimplant of Claim 125 configured and dimensioned as a cylinder.

134. (New) The osteoimplant of Claim 125 configured and dimensioned as an intervertebral insert, a long bone, a cranial bone, a bone of the pelvis, a bone of the hand, a bone of the foot or section of any of the foregoing.

Please cancel claims 8, 22, 44, 62 and 81 without prejudice.

REMARKS

Claims 1-134 are pending. Claim 1 has been amended to specify the compression strength of the solid aggregate of the bone-derived elements of the osteoimplant; dependent claims 8, 22, 44, 62 and 81, which previously contained the compression strength, have been canceled, so no new matter has been introduced by this amendment.

Applicants have taken note of the Examiner's willingness to allow certain claims (i.e., Claims 24-33, 46-55, 64-73, and 83-92) if a Terminal Disclaimer is provided and the claims are rewritten in the ways proposed by the Examiner. Applicants have provided a Terminal Disclaimer and have added new claims 95-134, which are Claims 24-33, 46-55, 64-73, and 83-92 rewritten as suggested by the Examiner (new Claims

95-104 correspond to original Claims 24-33; new Claims 105-114 correspond to original Claims 46-55; new Claims 115-124 correspond to original Claims 64-73; and new Claims 125-134 correspond to original Claims 83-92). Based upon these amendments, applicants believe that Claims 95-134 are in form for allowance, formal notification thereof being respectfully requested.

The Examiner has objected to the Specification for failing to reference continuing data for the present application. The specification has been amended to provide such a reference. Accordingly, withdrawal of the objection is respectfully requested.

The Examiner has rejected Claims 1-94 for obviousness-type double patenting over Claims 1-72 of commonly assigned Boyce et al. U.S. Patent No. 6,123,731 ("Boyce et al."). The Examiner has advised that a terminal disclaimer previously submitted on February 12, 2002 does not comply with 37 C.F.R. 1.321(b) because it does not include a statement by the person signing the disclaimer of the extent of his/her interest. While applicants respectfully submit that such a statement was included (see page 2, lines 4-5 of the prior terminal disclaimer), a revised terminal disclaimer accompanies this amendment, which applicants respectfully submit obviates the above obviousness-type double patenting rejection.

The Examiner has maintained the rejection of Claims 1-11, 13, 14, 19-23, 34-45, 56-63, 74-82 and 93-94 under 35 U.S.C. §102(b) for anticipation by Lyle U.S. Patent No. 5,061,286 ("Lyle"). According to the Examiner, Lyle discloses demineralized bone particles (which, of course, possess surface-exposed collagen) that are "linked together" with a binder such as cyanoacrylate.

While the Lyle demineralized bone particles possess surface-exposed collagen, there is not the slightest hint anywhere in this disclosure of the demineralized bone particles being "bonded to each other through chemical linkages between their surface-exposed collagen". The Lyle binding agents, e.g., cyanoacrylate of which the Examiner has taken particular note, bind the demineralized bone particles together. However, the function of cyanoacrylate in Lyle (and that of all the other binding agents disclosed in the patent) is essentially that of an adhesive. One skilled in the art reviewing Lyle would clearly recognize that cyanoacrylate adhesives as disclosed therein, even if applied in monomeric form, would polymerize *in situ* to form a polymerized adhesive. See, e.g., U.S. Patent Nos. 3,527,841 (cyanoacrylate adhesive is usually applied in monomeric form, with polymerization in situ to provide desired adhesive bond); 5,266,608 (cyanoacrylates are known adhesive reagents for bones which polymerize when applied to tissue surfaces); 5,328,687 ("Typically, when used as adhesives and sealants, cyanoacrylates are applied in monomeric form to the surfaces to be joined or sealed, where, typically, in situ anionic polymerization of the monomer occurs, giving rise to the desired adhesive bond or seal"); 6,306,243 (same); 6,174,919 (cyanoacrylate monomers and polymers formed therefrom useful as tissue adhesive in setting fractured bone structures) (copies of these patents are attached hereto as Exhibits 1-5, respectively).

There is no disclosure or suggestion of the Lyle binding agent chemically modifying the surface exposed collagen of the demineralized bone particles such that chemical linkages are formed *between the surface-exposed collagen* of adjacent demineralized bone particles. In lacking any disclosure or suggestion of such

chemical linkages, Lyle fails to anticipate or render obvious the subject matter of any of Claims 1-94.

The Examiner has maintained the rejection of Claims 1-5, 7, 11-14, 16, 19-21, and 34-35 under 35 U.S.C. §102(b) for anticipation by Jefferies U.S. Patent No. 4,394,370 ("Jefferies").

According to the Examiner, Jefferies discloses demineralized bone particles whose surface-exposed collagen is crosslinked, thereby inherently improving the mechanical strength of the resulting product.

However, Claim 1 and all of the remaining claims presented herein now recite that where *substantially all* of the bone-derived elements are substantially completely demineralized bone-derived elements, the osteoimplant contains at least one additional component selected from the group consisting of reinforcing particles and fillers, such that the solid aggregate of bone-derived elements possesses a compression strength of from about 10 to about 200 MPa. The Jefferies demineralized bone particles are substantially completely demineralized bone particles, i.e., they contain little if any of their original mineral content, primarily made up of calcium compounds. This being the case, the Jefferies grafting implant lacks any significant mineral content that would elevate its mechanical strength beyond that of the aggregated demineralized bone particles themselves.

Contrary to the Examiner's assertion, the collagen or macromolecules (which are, in fact, enzymes) of Jefferies cannot properly be considered a filler, as the purpose of these components in the Jefferies graft is either the formation of a sponge (when collagen is used) and the modification or acceleration of the osteogenic

properties of the materials (when the macromolecules are added). Moreover, Jefferies' recitation of collagen, in addition to the demineralized bone particles, is redundant as demineralized bone particles are, in essence, collagen. See, e.g., Lehman et al. "Recent advances in bone grafting", *Current Opinion in Orthopedics*, 7; VI:71-74 (1996) (the process of demineralizing bone leaves behind protein, bone growth factors, and collagen; demineralized bone lacks structural rigidity) (a copy of this article, obtained on the internet at www.medlib.iupui.edu/bcr/recadv.htm, is attached hereto as Exhibit 6; the text supporting the above assertion is found on p.3 of Exhibit 6). Accordingly, contrary to the Examiner's assertion, neither of these components may properly be considered the separate filler of applicants' invention as neither will provide the compression strength of applicants' osteoimplant.

Moreover, neither the collagen nor the macromolecules of Jefferies would improve the mechanical properties of the aggregated demineralized bone particles as the reinforcing particles of applicants' invention.

As previously noted, there is not the slightest suggestion in Jefferies of incorporating a reinforcing component of any kind into the grafting implant -- Jefferies' grafting implant is not intended to be used in circumstances where it can be expected to sustain relatively high mechanical loads. Thus, at column 2, lines 39-45, Jefferies discloses that implants according to the invention (referred to in the cited passage as "complexes") can be made into "thin membranes", "gels" or "preferably in a sponge-like configuration". These final products by their very nature are not intended to withstand high mechanical stresses. As noted above, demineralized bone is, essentially, collagen and the macromolecules of Jefferies are enzymes.

In contrast to Jefferies' products, applicants' osteoimplant as recited in the amended claims must possess some component which, in effect, imparts mechanical strength to crosslinked bone elements which is above and beyond that of merely crosslinked substantially completely demineralized bone elements. This mechanical strength-supporting component can be provided by the mineral content of superficially demineralized bone-derived elements (when such are employed) or when such mineral content is absent, or nearly absent, some added reinforcing particles/fillers. Due to this arrangement, applicants' osteoimplant can be used to repair or replace a variety of bones where mechanical strength of the osteoimplant is a practical consideration, as the solid aggregate of bone-derived elements which make up the osteoimplant possess a compression strength of from about 10 to about 200 MPa. See, for example, the disclosure at pages 13 and 14 of the specification.

In view of the foregoing, amended Claims 1-94 are believed to be both novel and nonobvious over the Jefferies disclosure.

The Examiner has maintained the rejection of Claims 12 and 15-18 under 35 U.S.C. §103(a) for obviousness over Lyle. The Examiner characterizes Lyle's "cyanoacrylate" as a crosslinking agent. However, as noted above in connection with the Examiner's rejection of the claims for supposed anticipation by Lyle, cyanoacrylate is a monomer which provides a polymer, the polymer being the actual adhesive which binds the Lyle demineralized bone particles together. There is no disclosure or suggestion in Lyle that cyanoacrylate functions in any other way.

In the absence of any indication in Lyle that the demineralized bone particles therein are bonded to each other through chemical bonds formed in their collagen-

exposed surfaces, amended Claims 1-94 can only be regarded as nonobvious, and therefore patentable, over Lyle.

In view of the foregoing amendments and remarks, early and favorable consideration of all the claims of the application, i.e. Claims 1-134, is respectfully requested.

Respectfully submitted,

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MARKED UP VERSION OF THE AMENDED CLAIMS

1. (Twice Amended) An osteoimplant which comprises a solid aggregate of bone-derived elements selected from the group consisting of superficially demineralized bone-derived elements, substantially completely demineralized bone-derived elements and mixtures thereof, adjacent bone-derived elements being bonded to each other through chemical linkages between their surface-exposed collagen, provided, that where substantially all of the bone-derived elements are substantially completely demineralized bone-derived elements the osteoimplant contains at least one additional component selected from the group consisting of reinforcing particles and fillers, and wherein the solid aggregate of bone-derived elements possesses a compression strength of from about 10 to about 200 MPa.

Exhibit 1

United States Patent Office

3,527,841
Patented Sept. 8, 1970

3,527,841

ALPHA-CYANOACRYLATE ADHESIVE COMPOSITIONS

Thomas H. Wicker, Jr., and John M. McIntire, Kingsport, Tenn., assignors to Eastman Kodak Company, Rochester, N.Y., a corporation of New Jersey

No Drawing. Filed Apr. 10, 1968, Ser. No. 720,326
Int. Cl. A61b 17/04; C08f 3/62; C08g 17/02
U.S. Cl. 260—823 11 Claims

ABSTRACT OF THE DISCLOSURE

Alpha-cyanoacrylate adhesive compositions for general and particularly for surgical uses containing poly(lactic acid) as a viscosity modifier and an acidic component such as SO_2 and/or a free radical scavenger such as hydroquinone as a polymerization inhibitor.

This invention relates to alpha-cyanoacrylate adhesive compositions for general and particularly for surgical uses. More particularly the invention relates to alpha-cyanoacrylate adhesive compositions containing poly(lactic acid) as a viscosity modifier.

The efficacy of the esters of alpha-cyanoacrylic acid as adhesives for general industrial and other uses is well known, having been described and claimed in numerous U.S. and foreign patents and in the literature. More recently, the medical and patent literature has disclosed that certain of these alpha-cyanoacrylates can be successfully used in many surgical applications as, for example, in the setting of fractured bone structures, as substitutes for, or adjuncts to, surgical sutures, in retarding the flow of blood from wounds and as aids in the repair and regrowth of living tissue generally. One of the problems encountered in the uses of these compositions, both as industrial and as surgical adhesives, has been control of the viscosity or flowability of the adhesive when applied to surfaces to be bonded or otherwise treated.

To take a typical example, when an alpha-cyanoacrylate such as methyl alpha-cyanoacrylate, probably the best known and most widely used cyanoacrylate adhesive, is applied to surfaces to be joined, it is usually applied in its monomeric form, and the resultant polymerization of the ester in situ gives rise to the desired adhesive bond. However, the ester in this form is too fluid at ordinary temperatures to be controllable for certain applications. It is, therefore, necessary to provide a means of controlling the viscosity or flowability of the composition. This is accomplished by adding a viscosity modifier or thickener to the monomeric material.

In certain industrial applications a relatively high degree of fluidity may not be objectionable and may even be desirable, but for other industrial uses and for surgical uses, the viscosity of flowability of the composition must be controlled in order to prevent undue escape of the adhesive from any given area to which it is applied as well as to allow sufficient time for the monomeric material to polymerize and thus to bring about the desired bonding action.

The problem here dealt with has already been generally recognized by workers in this field and a rather wide variety of viscosity modifiers for alpha-cyanoacrylate adhesives have been suggested in patents and the literature. The present invention relates to a viscosity modifier, not heretofore known to the art, for use as a component of this type of adhesive and having unique solubility in alpha-cyanoacrylates and an unusually high order of heat stability. These properties render such modifiers particularly advantageous when used as components of surgical adhesives which must be subjected to relatively high heat

sterilization procedures in order to provide that the resulting compositions shall be absolutely sterile and safe for their intended uses.

Another requirement of alpha-cyanoacrylate adhesive compositions which are to be employed for surgical uses is that both the adhesive component and the viscosity modifier must be relatively non-toxic and each component must be biodegradable, that is, each must be susceptible of biochemical transformation or degradation which will result in harmless products which can be readily absorbed into and carried away from the point of application by the body fluids and thus ultimately eliminated from the system. As will be more fully set forth hereinafter, the adhesive compositions or the present invention fully meet these requirements.

This invention has as an object to provide alpha-cyanoacrylate adhesive compositions having viscosity and other characteristics which render them outstandingly useful as adhesives.

A further object is to provide alpha-cyanoacrylate adhesive compositions having viscosity and other characteristics which render them particularly useful for surgical applications.

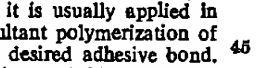
A further object is to provide alpha-cyanoacrylate adhesive compositions particularly adapted for use in the surgical field and characterized by the fact that both the adhesive and the viscosity modifying components are biodegradable.

A further object is to provide alpha-cyanoacrylate adhesive compositions for both general and surgical uses containing a viscosity modifier which is soluble in a wide range of the esters of alpha-cyanoacrylic acid and having a high degree of stability under heat sterilization conditions.

A still further object is to provide alpha-cyanoacrylate adhesive compositions containing a biodegradable viscosity modifier and stabilized against polymerization by the presence therein of a polymerization inhibitor.

Other objects will appear hereinafter.

These objects are accomplished by the following invention which comprises adding to a monomeric ester of alpha-cyanoacrylic acid having the general formula:



wherein R is an alkyl group of 1–16 carbon atoms, an alkoxyalkyl group, an acyloxyalkyl group, a haloalkyl group, an arylalkyl group, a cyanoalkyl group, a cyclohexyl group, a phenyl group or an alkenyl group of 2–16 carbon atoms, as a viscosity modifier up to 25 percent by weight, based on the weight of the monomeric ester, of poly(lactic acid). The preferred range of the viscosity modifier is from 1 to 5 percent by weight.

Typical monomeric alpha-cyanoacrylates suitable for use in the adhesive composition of our invention are the methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, n-amyl, isoamyl, 3-acetoxypropyl, 2-methoxyethyl, 3-methoxypropyl, 3-chloropropyl, benzyl, phenyl, and alkenyl alpha-cyanoacrylates.

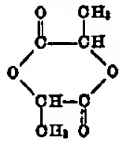
The alpha-cyanoacrylate esters can be produced by the procedure of the U.S. patent to Joyner and Hawkins, 2,721,858, involving reaction of an alkyl cyanoacetate with formaldehyde in a non-aqueous organic solvent and in the presence of a basic catalyst, followed by pyrolysis of the anhydrous intermediate polymer in the presence of a polymerization inhibitor. The alpha-cyanoacrylate monomers prepared with low moisture content and essentially free of impurities have the best activity for surgical use. Another suitable process for preparing such alpha-cyanoacrylate esters is that described in the U.S. patent to Hawkins and McCurry, 3,254,111.

In order to stabilize the compositions of our invention against too rapid polymerization in use, and also to give them a satisfactory shelf life, one or more polymerization inhibitors may be employed. The inhibiting material may be an acidic stabilizer or a free radical scavenger. In some cases, both an acidic stabilizer and a free radical scavenger may be employed if desired. A free radical scavenger may be defined as a material which has the ability to react with an unpaired electron to produce a substance which does not initiate further polymerization.

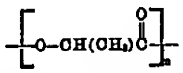
Examples of acidic stabilizers useful in the adhesive compositions of our invention are: sulfur dioxide, nitrogen oxide, phosphoric acid, phosphorous acid, boron trifluoride, organic acids having a pKa of 1 to 3, and polyphosphoric acid. For adhesive compositions designed for general or industrial uses, the stabilizer may be present to the extent of .0005–.06 percent by weight of the total composition, the preferred range being .0005–.003. In compositions designed for surgical uses, the stabilizer may be present in amounts within the range of .004–.25 percent by weight.

Among the free radical scavengers which may be employed as stabilizers in the adhesive compositions of our invention may be mentioned: hydroquinone, monomethyl ether of hydroquinone, butylated hydroxyanisole, butylated hydroxytoluene and t-butyl hydroquinone. For adhesive compositions designed for both general and surgical use, the free radical scavenger may be present to the extent of .001–.15 percent by weight of the total composition, the preferred range being .08–.12 percent.

The poly(lactic acid) component employed as the viscosity modifier in accordance with our invention may be prepared by polymerizing lactide



and has the repeating unit



in which the identity of the end groups is not known. Its preparation is described in U.S. Army Medical Biomechanical Research Laboratory Technical Report No. 6608 entitled "Poly(lactic acid) for Surgical Inplants" (obtainable as Document AD 636,716 from Clearinghouse for Federal, Scientific and Technical Information, Department of Commerce, Washington, D.C.). The polymer can be prepared in a range of molecular weights by choice of catalyst or catalyst concentration, monomer purity, reaction time and temperature. This polymer is biodegradable and we have found that it is quite unexpectedly very soluble in methyl-2-cyanoacrylate and its higher alkyl homologues.

In formulating adhesive compositions in accordance with our invention, the concentration of poly(lactic acid) in the monomeric alpha-cyanoacrylate may, as indicated above, be within the range of 1–25 percent by weight of the total composition. The amount of the poly(lactic acid) employed in any given composition will depend on the inherent viscosity of the particular polymer employed. In general, a polymer having an I.V. within the range of .5–2 is satisfactory but polymers of higher I.V. may be employed if desired.

The following examples are included for a better understanding of the invention.

EXAMPLE 1

To 10.00 g. of methyl 2-cyanoacrylate is added 0.50 g. of poly(lactic acid) having an inherent viscosity of 2.04. The mixture is tumbled in a sealed glass container for three hours at 70° C. to complete solution. The viscosity of the resulting solution is found to be 85 cp. The solution is then sterilized at 125° C. for 1 hour giving a solution with slightly decreased viscosity.

EXAMPLE 2

A 5% solution of poly(lactic acid) in butyl 2-cyanoacrylate is prepared by dissolving 0.50 g. of poly(lactic acid) (I.V.=2.04) in 10.00 g. of butyl 2-cyanoacrylate and tumbling for three hours at 70° C. The solution is found to have an initial viscosity of 89 cp. Upon sterilization at 140° C. the viscosity decreases slightly.

EXAMPLE 3

Ten grams of isobutyl 2-cyanoacrylate containing 0.01 g. of hydroquinone is thickened with 0.50 g. of poly(lactic acid) (I.V.=2.04) to give a solution with a viscosity of 110 cp. The solution is then sterilized at 140° C. for one hour. The solution viscosity is found to be 114 cp. after sterilization.

EXAMPLE 4

Five grams of a high I.V. poly(lactic acid) (I.V.=2) is dissolved in 100 g. of n-hexyl 2-cyanoacrylate. The initial solution viscosity is approximately 80 cp. Upon sterilization at 150° C. a clear, viscous formulation is obtained which is suitable for surgical purposes.

EXAMPLE 5

A solution having an initial viscosity of approximately 80 cp. is obtained when 7.0 g. of a medium I.V. poly (lactic acid) (I.V.=1.2) is dissolved in 100 g. of 3-methoxybutyl-2-cyanoacrylate by tumbling at 70° C. for three hours. No change in viscosity is noted after sterilization for one hour at 130° C.

EXAMPLE 6

A 12% solution of low I.V. poly(lactic acid) (I.V.= 0.5) in ethyl 2-cyanoacrylate has a viscosity of approximately 100 cp. Heat sterilization at 130° C. gives a clear, stable, viscous solution suitable for surgical purposes.

EXAMPLE 7

A high I.V. poly(lactic acid) (I.V.=2) is acylated by treating with an acetic anhydride-acetic acid mixture. The resulting end-capped polymer is dissolved in butyl 2-cyanoacrylate. Five percent of the polymer is required to give a solution viscosity of approximately 80 cp. The solution viscosity does not change on sterilization for one hour at 140° C.

EXAMPLE 8

Five grams of a high I.V. poly(lactic acid) (I.V.~2) is dissolved in 95 g. of n-decyl 2-cyanoacrylate. The initial solution viscosity is about 82 cp. Upon sterilization at 150° C. a clear, viscous formulation is obtained which can be used for surgical purposes.

The alpha-cyanoacrylate adhesive compositions of our invention are distinguished from all previously known alpha-cyanoacrylate adhesive compositions by the presence therein of a viscosity modifier comprising poly(lactic acid). As indicated above, this modifier is unique in that it is soluble in the entire range of alkyl esters of 2-cyanoacrylic acid and possesses such heat stability characteristics that the resulting viscous solution in the alpha-cyanoacrylic component can be heat sterilized to provide sterile, biodegradable surgical adhesives, as well as adhesives for general industrial use.

These viscous adhesive compositions have a number of advantages over the water-thin monomeric materials which have been used heretofore in tissue adhesive applications. A primary advantage of the viscous adhesives of our invention is that the placement of the adhesive in the body can be more accurately controlled since the tendency of the material to run after application to the site is considerably reduced. Another feature of our viscous adhesives is that they are completely clear and free of cloudy material

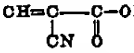
even after a heat sterilization treatment at 125–150° C. or even higher. An additional advantage of cyanoacrylate surgical adhesives thickened with poly(lactic acid) is that these adhesives exhibit a high order of stability in the heat sterilizalton treatment. While we rely on no theory to explain this high order of stability, it may be that the polymeric material undergoes hydrolysis in the presence of adventitious moisture to create stabilizing acid groups.

While the emphasis in the above description of our invention has been laid on a process for preparing sterile cyanoacrylate adhesive compositions particularly adapted for surgical applications, it will, of course, be understood that such compositions are adapted for a wide variety of industrial and other applications in which the sterile nature of the composition is not of importance.

Although the invention had been described in considerable detail with particular reference to certain preferred embodiments thereof, variations and modifications can be effected within the spirit and scope of the invention as described hereinabove, and as defined in the appended claims.

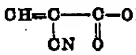
We claim:

1. An adhesive composition comprising at least 75 percent by weight of a monomeric ester of alpha-cyanoacrylic acid having the general formula:



wherein R is an alkyl group of 1–16 carbon atoms, an alkoxy-alkyl group, an acyloxyalkyl group, a haloalkyl group, an arylalkyl group, a cyanoalkyl group, a cyclohexyl group, a phenyl group or an alkenyl group of 2–16 carbon atoms and, as a viscosity modifier, up to 25 percent by weight of poly(lactic acid).

2. The composition of claim 1 in which the monomeric ester of alpha-cyanoacrylic acid has the general formula:



wherein R is an alkyl group of 1–10 carbon atoms.

3. The composition of claim 2 containing at least about 95 percent by weight of the monoemric ester of alpha-cyanoacrylic acid and up to about 5 percent by weight of poly(lactic acid).

4. The composition of claim 1 which contains at least .0005 percent by weight of acidic stabilizer.

5. The composition of claim 1 which contains at least .001 percent by weight of a free radical scavenger.

6. The composition of claim 3 which contains at least .0005 percent by weight of an acidic stabilizer.

7. The composition of claim 3 which contains at least .001 percent by weight of a free radical scavenger.

8. The composition of claim 2 containing at least about 95 percent by weight of methyl 2-cyanoacrylate, up to about 5 percent by weight of poly(lactic acid) and at least .0005 percent by weight of an acidic stabilizer.

9. The composition of claim 2 containing at least about 95 percent by weight of methyl 2-cyanoacrylate, up to about 5 percent by weight of poly(lactic acid) and .001–.15 percent by weight of hydroquinone.

10. The composition of claim 2 containing at least about 95 percent by weight of isobutyl 2-cyanoacrylate, up to about 5 percent by weight of poly(lactic acid) and at least .0005 percent by weight of an acidic stabilizer.

11. The composition of claim 2 containing at least about 95 percent by weight of isobutyl 2-cyanoacrylate, up to about 5 percent by weight of poly(lactic acid) and .001–.15 percent by weight of hydroquinone.

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C. A. HENDERSON, JR., Assistant Examiner

U.S. Cl. X.R.

128—92, 334; 260—78.3, 78.4

Exhibit 2

US005266608A

United States Patent [19]

Katz et al.

[11] Patent Number: 5,266,608

[45] Date of Patent: Nov. 30, 1993

[54] BIOMEDICAL ADHESIVE COMPOSITIONS

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[73] Assignees: Technion Research & Dev't Foundation, Ltd., Israel; GBF Gesellschaft fur Biotechnologische Forschung, Fed. Rep. of Germany

[21] Appl. No.: 722,088

[22] Filed: Jun. 27, 1991

[30] Foreign Application Priority Data

Jun. 29, 1990 [IL] Israel 094910

[51] Int. Cl.[5] A61K 47/30

[52] U.S. Cl. 523/111; 523/113; 523/116; 523/118

[58] Field of Search 527/118; 523/113, 14, 523/111, 16; 528/65, 55, 56, 57, 58; 424/449; 525/453; 524/788

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Primary Examiner—Thurman K. Page
Assistant Examiner—P. Kulkosky
Attorney, Agent, or Firm—Morgan & Finnegan

[57] ABSTRACT

Novel non-elastomeric biomedical adhesive compositions for calcified tissues, are described. The compositions are characterized by a network structure which is obtained by the reaction of a polyisocyanate having at least two isocyanate groups with at least one polyol which possesses surface wetting properties with the participation of compounds selected from calcium and phosphorus, optional in the presence of a catalyst. The polyisocyanate is selected from aliphatic, alicyclic and aromatic compounds and preferred amounts are in the range of 20% to 80% by weight of the total amount of reactants. The polyol is selected from polyalkylene ether glycols and polyester glycols containing between 25 to 75 carbon atoms and preferred amounts are in the range of 10% to 80% by weight of the total amount of reactants. The adhesive compositions were found to produce a fast bonding of the calcified tissues, with a joint strength of above 0.5 N/sq.mm.

10 Claims, No Drawings

BIOMEDICAL ADHESIVE COMPOSITIONS

The present invention relates to adhesives compositions to be useful in biomedical applications. More particularly, the invention relates to new type of medical polymer adhesive compositions to be used in the treatment of bone fractures and for gluing of calcified body tissues.

BACKGROUND OF THE INVENTION

Various adhesive compositions were suggested in the last thirty years to replace the conventional metal assisted osteosynthesis method which uses various devices such as screws, plates and nails, in the treatment of fractures. Such compositions may offer a number of advantages over the conventional method such as bonding of particular fractures, ease and speed of fixation of fractures, excessive stiffness of current metal plates while providing a rigid fixation, etc.

Adhesive compositions to be useful for biomedical applications should respond to a quite large number of criteria such as:

- to be inert;
- to be non-toxic by itself or by its degradation products;
- to be non-carcinogenic and non-allergenic at long and short term;
- to be absorbed within the specific time of healing of the tissues that it binds;
- to allow the adjacent tissues to grow and unite through the adhesive barrier;
- to form a strong enough union which provides a uniform distribution of stresses over the entire applied area;
- to adhere quickly to moist tissues at body temperature;
- to be easily sterilizable, and
- to be economically satisfactory.

In the use of adhesives for biomedical applications, there are also other factors apart from the immediate bonding. Thus for instance, chemical interference by moisture (blood), or fat (lipids) can change the surface properties of adherents and will affect the wettability. Also, the changing nature of the substrate may give rise to different initial exothermic chemical reactions during the formation of the adhesive joint.

In the past few decades there have been several studies on the bonding strength between bone and different adhesives such as epoxy resins, polyurethanes, polyacrylates, polymethacrylates and composite resins used in dentistry. A brief review of some specific prior references is hereafter presented.

Polyurethanes were extensively investigated about thirty years ago as adhesive reagents for bones. However, it was concluded that their use was not satisfactory for this application [G. Meyer et al, Biomat.Med.-Dev.Art Org. 7(1), 55-71, 1979].

Alkyl-2-cyanoacrylates were also suggested and found to polymerize quite rapidly when applied to dry tissue surfaces. However, due to the exothermic polymerization and toxic degradation products, necrosis of surrounding tissue has been observed. Furthermore, it was found that these adhesives formed an impenetrable barrier between adjacent tissues thus interrupting the natural healing processes until biodegradation was accomplished.

In a very recent paper (J. Kilpikari et al, J. of Biomedical Materials Research, 20, 1095-1102, 1986) there are reported results on the bonding strength of alkyl-2-cyanoacrylates to bone in vitro. Although initially, the strength was quite high, it decreased after three weeks. According to the U.K. Patent No. 1,489,163 adhesive compositions for soft body tissues are suggested, being prepared from an aromatic diisocyanate, a macrodiisocyanate of a particular formula and 2,4,6-tris-(dimethylaminomethyl)phenol. Such adhesives are mentioned that were tested for effectiveness in the gluing of soft tissues of animal, in plastic repair of aponeurosis of the anterior abdominal wall and for reinforcing a cerebral aneurysm. A highly elastic porous polymeric film was formed on the vessel surface.

According to the European patent application No. 244,688 there are provided adhesive formulations for biomedical applications comprising: (a) a polyphenolic protein component of a specific decapeptide formula; (b) a cross-linking agent for the decapeptide; (c) a surfactant functioning as a spreading agent, and (d) a filler compatible with the intended use. Preferred surfactants which are suggested are sodium dodecylsulfate and sodium-dodecylsulfonate. The ratios between the above components depend according to the specific use intended for said compositions, e.g. biomedical adhesive in orthopedic repairs, ophthalmic adhesive for healing perforations, attachement of lenses or corneal components parts, dental adhesive to hold crown in place, medical adhesive for attachement of soft tissues, etc.

According to U.S. Pat. No. 4,740,534 surgical flexible adhesive with improved elasticity are obtained by a reaction betwen at least one NCO-terminated hydrophilic urethane, derived from a polyisocyanate and a polyol, and at least one unsaturated cyanoacrylate compound containing a cyano group attached to a carbon atom constituting the polymerizable double bond. The results submitted in the patent show that very fast curing times are achieved, but nothing is mentioned therein regarding the strength of the bonding which was obtained. The adhesives are supposed to be particularly useful for tisues such as blood vessels, heart, lung, esophagus, stomach, skin and the like.

The above brief review illustrates the long felt want for obtaining biomedical adhesive compositions for soft and calcified tissues which could be able to replace the conventional metal osteosynthesis devices.

It is an object of the present invention to provide new biomedical adhesive compositions for calcified tissues. It is another object of the present invention to provide new biomedical adhesive compositions for calcified tissues which are biocompatible and biodegradable. It is a further object of the present invention to provide new biomedical adhesive compositions which provide adequate tensile strengths during the time of healing of the treated fracture. It is yet another object of the present invention to provide biomedical adhesive compositions which are not interfering with the natural healing proccess of the injured bone.

BRIEF DESCRIPTION OF THE INVENTION

The invention relates to non-elastomeric biomedical adhesive compositions for calcified tissues consisting of a network to be obtained by the reaction of a polyisocyanate having at least two isocyanates groups, in an amount which ranges between 20% to 80% by weight of the total amount of reactants with at least one polyol which possesses surface wetting properties in amount of

between 10% to 80% by weight of the total amount of reactants with the participation of compounds containing calcium and phosphorus, optional in the presence of a catalyst. The adhesive compositions according to the present invention were found to be stable in a phosphate buffered solution at 37° C. and susceptible to enzymatic degradation. It was found that the network formed in the reaction between the constituents does occur even without a promoter for crosslinking.

The temperature required for the reaction is the ambient one or slightly above, but it does not surpass a maximum temperature of above 42° C. Since the reaction is slightly exothermic, no external heating is generally required. An important property of the adhesive compositions, according to the present invention, is the relatively fast strength imparted in gluing of bone tissues which is not affected by the presence of blood or moisture from a biological fluid. As known, the living tissue is very complex, being characterized by a mosaic structure composed of alternating hydrophilic sections. Consequently, hydrophilic and hydrophobic interactions have to be considered in selecting a proper composition. The mechanism which governs the gluing operation might be explained by the interaction of the adhesive at the hydrophilic sections of the tissue, when it does displace moisture from these sections creating a strong adhesion joint. The healing process does occur in the living tissue after gluing. It seems that the structure of the adhesive joint resulting from the use of the compositions according to the present invention, does not prevent this healing process and even contribute to this process under optimum conditions, due to fixation of the bone fragments and their proper location as found from some in-vivo experiments.

The reagents possessing a diisocyanate ot triisocyanate groups useful for the present invention may be selected from a large number of aliphatic, alicyclic and aromatic compounds and some illustrative examples are as follows: 4,4',4''-triphenylmethane triisocyanate, tolylene 2,4-diisocyanate, tolylene 2,6-diisocyanate or any mixture thereof; 1,3-phenylene diisocyanate, 1,4-phenylene diisocyanate, 1,12-diisocyanatododecane, 1,6-diisocyanatohexane, isophorone diisocyanate, each of them either alone or any combinations thereof, etc.

The polyol constituent may be selected from broad classes of compounds which comprise polyalkylene ether glycols, polyester glycols, preferably being those containing between 10 and 80 carbon atoms and most preferably between 25 and 55. Some illustrative examples of useful polyol constituents are as follows: sorbitan monolaurate, sorbitan monostearate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monooleate, sorbitan monopalmitate, octyl gallate, hexyl resorcinol, glycol monostearate, lauryl gallate, sorbitan monolaureate, polyoxyethylene (20) sorbitan monolaureate, polyoxyethylene (20) sorbitan monostearate, acting by themselves or by any mixture thereof. It was found that the wetting properties of the polyol are absolutely required in order to obtain the adhesive compositions according to the present invention. When a polyol which does not possess these properties was used, the adhesive property was very poor (see comparative Example 12).

As additional polyols which may be added to participate in the reaction, the following are mentioned: glycerol, ethylene glycol, polyethylene glycol, polypropylene glycol, polytetrahydrofuran, polycaprolactone diol, polycaprolactone triol, etc.

Among the constituents which were found to participate in the reaction for obtaining the adhesive compositions according to the present invention, there are those compounds containing calcium and phosphorus. In an experiment carried out without the incorporation of these compounds, the strength of the joint resulted with the adhesive composition was found to be very weak (see comparative Example 11). It seems that these compounds contribute to a large extent to the network resulted in the adhesion of the calcified tissue and to the joint strength. Some illustrative examples of a few compounds found to be useful by their presence are as follows: tricalcium phosphate, hydroxyapatite in its pure form or containing traces of magnesium or sodium, esters of calcium salts of phosphoric acids such as: calcium salt of phosphorglyceric acid, glucose-6-calcium salt of phosphoric acid, glucose-1-calcium salt of phosphoric acid and calcium salt of D(-)3 phosphoglyceric acid.

The catalyst useful for the reaction may be selected from the broad classes of compounds, as known in the art for this purpose. Some typical examples are: sodium trichlorophenate, sodium tetrachlorophenate, sodium pentachlorophenate, ferric 2-ethylhexanoate, ferric acetylacetonate, dibutyltin di-2 ethylhexanoate, stannous 2-ethylhexanoate, cobalt 2-ethyl-hexanoate, etc.

The adhesive compositions according to the present invention may contain, if necessary, various additives provided that they are compatible with human tissues, such as: fillers selected from carbon black, metal oxides, silicates, various ceramic powders, acrylic and methacrylic resin powders; stabilizers such as diphenyl-p-phenylene diamine, trimethyldihydroquinone, plasticizers, etc. All these agents are not participating in the reaction which does produce the network of the adhesive composition.

One of the characteristics of the adhesive compositions is the high porous structure with open pores. The existence of the high porous structure is of great importance in the bone healing process. One of the advantages of the glue compositions is the fact that the setting of the adhesive takes place after a short period of time, which generally is in the order of a few minutes.

The adhesive compositions according to the present invention were found to produce fast bonding of the calcified tissues, joint strength of at least 0.2 N/sq.mm and generally joint strength of above 0.5 N/sq.mm being achieved Moreover, the bone joints formed with the adhesive compositions, immersed in phosphate buffered saline solution at 37° C. were found to be stable after prolonged periods of time. It was found that the surface wetness of bones on which the adhesive composition was applied did not weaken the tensile strength of this joint.

It was found that the adhesive compositions are biodegradable allowing growth of the new tissue soon after the surgery, fact which indicates the beginning of the healing process. No adverse reactions were found in tissues neither at the operation site nor in internal organs (lymphomatic glands, spleen, lungs, liver and kidney) after a period of seven months. This indicates biocompatibility of the adhesive and of its degradation products. Tests carried out in-vivo, on the tibia of a dog, showed that the presence of the adhesive in the animal body caused neither inflammation nor major irritation of the tissue around the broken tibia. Also, no evolution of fever was detected in said dog. No adverse reactions were discovered in the animal after periods of up to six

months. The X-ray of a bone fracture taken two weeks after the gluing, shows that the adhesive prevented any dislocation of the fracture fragment. The presence of ingrowth of new connective tissue in the location of the adhesive, as shown by microscopic tissue examination, after decalcification of the operated bone, proved the beginning of healing process.

Among the main advantages of the bioadhesive compositions according to the present invention, the following can be mentioned:

- The constituents of the compositions possess adequate shelf life at ambient conditions.
- They can be produced easily in large scale.
- They are able to be sterilized by recognized methods.
- They can be packaged in a form allowing antiseptic handling and transfer.
- Their initial setting time is reasonable without affecting the normal time of surgery.

The invention will be herinafter illustrated by a number of Examples, being understood that no limitation should be implied by these Examples which are presented only for a better understanding of the invention.

It should be pointed out that Examples 10, 11 and 12 do not illustrate the present invention being presented for comparison purposes only.

In the Examples the concentrations are given in weight percentage unless otherwise stated.

EXAMPLE 1

An amount of 9.5 meq. of Ca-salt of phosphorglyceric acid was added to 4.8 meq. of polyoxyethy sorbitan monolaurate (Tween 20, Trade Mark produced by Atlas Chem) while stirring. After a thorough stirring, an amount of 46 meq. of tolylene diisocyanate (TDI) was added in portions. The mixture was stirred, followed by the introduction of 0.1 g of 2-ethyl-hexanoic acid tin salt as catalyst. The mixture was stirred and the adhesive, still liquid, was spread on the bone specimen by the use of a glass rod and held under the pressure of about 300 g for about 3 min. The strength of the bone joint, after immersion in a phosphate buffered saline solution at 37° C. for 4 days, was 0.31 N/sq.mm.

EXAMPLE 2

The experiment as in Example 1 was repeated using the same reagents and the same amounts, but without adding the catalyst.

The resulted adhesive composition was spread on the bone specimen by the use of a glass rod and held under the pressure of about 300 g for 15 minutes. The strength of the bone joint, after immersion in a phosphate buffered saline solution at 37° C. for 16 days was 0.94 N/sq.mm.

EXAMPLE 3

The experiment as in Example 1 was repeated using the same reagents and catalyst and the same amounts, except the amount of TDI which in this experiment was 13.7 meq. instead of 46 meq.

The resulted adhesive composition was spread on the bone specimen by the use of a glass rod and held under the pressure of about 300 g for about 5 minutes. The strength of the bone joint, after immersion in a phosphate buffered saline solution at 37° C. for 16 days was 0.27 N/sq.mm.

EXAMPLE 4

An amount of 9.5 meq. of glycerophosphate calcium salt was added to 4.6 meq. of polyoxyethylenesorbitan monooleate (Tween 80, Trade Mark produced by Atlas Chem.) while stirring. After about 24 hours of stirring, 46 meq of TDI was added in portions. After the last addition of the TDI, the mixture was thoroughly stirred, followed by the introduction of 0.1 g of 2-ethyl-hexanoic acid tin salt. The mixture was again stirred and the adhesive, still liquid, was spread on the bone specimens by the use of a glass rod and held under a pressure of about 300 g for 5 minutes. The strength of the bone joint, after immersion of one day in a phosphate buffered saline solution at 37° C. was 0.31 N./sq.mm.

EXAMPLE 5

The experiment as in Example 4 was repeated using the same reagents and amounts except the following: TDI was replaced by 32 meq. of 4,4'-diphenylmethyl-diisocyanate (MDI) and 4.6 meq. of Tween 80 was replaced by 4.9 meq. of Tween 20 (Trade Mark produced by Atlas Chem). The reaction conditions and the testing of the bone joint were the same as in Example 4, the strength of the bone joint was 0.39 N/sq.mm.

EXAMPLE 6

The experiment as in Example 1 was repeated using the same reagents and amounts, except that 2.0 g of hydroxyapatite was used instead of 9.5 meq. of the calcium salt of phosphorglyceric acid. The reaction conditions were the same as in Example 1.

The adhesive composition was spread on the bone specimens by the use of a glass rod and held under a pressure of about 300 g for about 5 minutes. The strength of the bone joint after immersion of 2 days in a phosphate buffered saline solution at 37° C. was 0.43 N/sq.mm.

EXAMPLE 7

The experience as in Example 1 was repeated using the same reagents except that 4.7 meq. of polyoxyethylenesorbitan monopalmitate (Tween 40 Trade Mark produced by Atlas Chem) were used instead of the Tween 20. The same amounts of reagents were used, except that only 0.02 g of the catalyst were added.

The adhesive composition was spread on the bone specimen, and tested as described in Example 6. The strength of the bone joint was 0.9 N/sq.mm.

EXAMPLE 8

An amount of 9.5 meq of calcium salt of phosphorglyceric acid was added under stirring to a mixture of 3.5 meq of Tween 40 and 16.3 meq of glycerine. After 24 hours of stirring, 38 meq of TDI were added in a single portion. No catalyst was added in this experiment. The mixture was stirred for less than 1 minute and the adhesive, still liquid, was spread on the bone specimens by the use of a glass rod and held under a pressure of about 300 g for 5 minutes. The strength of the bone joint after immersion of 2 days in a phosphate buffered saline solution at 37° C. was 0.6 N/sq.mm.

EXAMPLE 9 (In-Vivo Adhesion)

The surgery was performed on a dog (18 kg) anesthetized with Nembutal (30 mg/kg). Preparation of the operative area included shaving and washing the skin with Betadine. A 5 cm incision of the cutis was made in

the mid third of the tibia, followed by opening of the deep fascia and separation between the subperiosteum and the bone.

From the front of the tibia a cortical slice, with a square base of 0.7 cm×0.7 cm, was removed.

A small amount of the glue, as obtained in Example 1, was spread on the tissue around the exposed bone, following a process of the site cleaning, and the bond fragment was replaced in its original position. The dermis was closed and the leg was bandaged and placed in a plaster of Paris cast.

Six weeks later the surgical procedure was repeated on the dog and the tibia was exposed. It was found that the tissues close to the adhesion site were not inflamed or infected. The fragment which was glued on six weeks before was still in place. Attempts to remove the fragment by forceps did not succeed.

EXAMPLE 10 (Comparative)

The experiment as in Example 1 was repeated but instead of the sorbitan an amount of 3.1 meq. of polyethylene glycol tert-octylphenyl ether (Triton 100, Trade Mark, produced by Rohm & Haas) was utilized.

The adhesive composition was spread on the bone fracture, in the same manner as in Example 1. No strength at all for the joint could be measured, after immersion in a phosphate buffered saline solution for 24 hours and the bone fracture was noticed.

EXAMPLE 11 (Comparative)

The experiment as in Example 1 was repeated using the same reagents and amounts, except the calcium salt of phosphorglyceric acid which was omitted.

The adhesive composition was spread on the bone fracture in the same manner as in Example 1. No strength at all for the joint could be measured, after immersion in a buffer solution for 48 hours and the bone fracture was noticed.

EXAMPLE 12 (Comparative)

The experiment as in Example 1 was repeated, but instead of polyoxyethylene sorbitan monolaureate (Tween 20), an equivalent amount of dextrin (i.e a polyol which does not possess wetting agent properties) was used.

It was found that this composition did not possess an adhesive property even after prolonged setting time.

EXAMPLES 13-23

A number of experiments were carried out using the general procedure and reaction conditions as described in the above Examples, using various polyols, polyisocyanates and compounds containing calcium and phosphorus.

The data of these experiments and the strength of the bone joint after immersion in a phosphate buffered saline solution at 37° C. are sumarized in the following Table.

Ex. No.	Polyol used	Isocyanate used	Ca-P compound.	Strength N/ sq. mm	after days
13[1]	4.8 meq A	63.2 meq a	16 meq L	0.52	2
14	7.6 meq B	46 meq b	4.7 meq L	0.43	3
15[2]	5.25 meq C	27.6 meq c	0.5 g N	0.24	3
16	6.15 meq D	16 meq c	2.3 meq L	0.39	1
17	7.05 meq E	9.0 meq e	0.5 g P	0.38	5
18	12.55 meq F	23 meq f	0.5 g N	0.4	2

-continued

Ex. No.	Polyol used	Isocyanate used	Ca-P compound.	Strength N/ sq. mm	after days
19	17 meq G	9.0 meq e	9.5 meq L	0.7	2
20	4.9 meq H	23 meq c	3.1 meq L	0.32	3
21	4.6 meq K	11.5 meq b	0.5 g N	0.34	5
22	4.8 meq A	16.6 meq h	9.5 meq L	0.37	1
23	4.8 meq A	27.6 meq b	4.1 meq R	0.46	3

[1]the reaction mixture was heated at 40° C.
[2]an amount of 0.05 g of 2-ethyl-hexanoic acid as catalyst was added and the polyisocyanate was added in two equal portions.
In the above Table the symbols for the reagents used in the various experiments are as follows:
A = polyoxyethylene sorbitan monolaureate (Tween 20)
a = hexamethylene diisocyanate.
L = Ca-salt of phosphorglyceric acid.
B = 2.8 meq of glycerol monostearate + 4.8 meq Tween 20.
b = 46 meq of tolylene diisocyanate (TDI, commercial mixture of isomers) added in two equal portions.
C = 3.4 meq of Tween 20 + 1.85 meq of polycaprolactone diol.
c = 27.6 meq of TDI added in two equal portions.
N = hydroxyapatite.
D = 1.15 meq of polycaprolactone diol + 5 meq of 4-hexyl resorcinol.
E = 5.2 meq of octyl gallate + 8.4 meq of polycaprolactone diol.
e = isophorone diisocyanate.
P = tricalcium phosphate.
F = 3.75 meq of poly-tetrahydrofuran + 8.8 meq of lauryl gallate.
f = 2,4 TDI (the pure isomers).
G = sorbitan monolaureate.
H = 3.1 meq Tween 20 + 1.8 meq sorbitan monooleate.
K = polyoxyethylene sorbitan monostearate
h = 4,4'4''-triphenylmethane triisocyanate (20% in a methylene chloride solution)
R = calcium salt of D(−3)-phosphoglyceric acid.

We claim:

1. A composition consisting of a network to be obtained by the reaction of a polyisocyanate having at least two isocyanate groups, in an amount which ranges between 20% to 80% by weight of the total amount of reactants with at least one polyol which possesses surface wetting properties in an amount of between 10% to 80% by weight of the total amount of reagents, with the participation of compounds containing calcium and phosphorus, said polyisocyanate being selected from the group consisting of aliphatic, alicyclic and aromatic polyisocyanates, said polyol being selected from the group consisting of polyalkylene ether and glycols containing between 25 and 55 carbon atoms, said compounds containing calcium and phosphorus being present in an amount sufficient to permit said adhesive composition to produce bonding of calcified tissues with a joint strength of at least 0.2 N/sq. mm., said composition being a non-elastomeric biomedical adhesive composition which is degradable by physiological enzymes and which is biocompatible.

2. The non-elastomeric biomedical adhesive composition according to claim 1, wherein said network is obtained in the presence of a catalyst.

3. The non-elastomeric biomedical adhesive composition according to claim 1, wherein said polyisocyanate is: tolylene 2,4-diisocyanate, tolylene 2,6-diisocyanate, 1,3-phenylene diisocyanate, 1,4-phenylene diisocyanate, isophorone diisocyanate, hexamethylene diisocyanate, 1,12-diisocyanatododecane, 1,6-diisocyanatohexane, 4,4',4''-triphenylmethane triisocyanate, mixtures thereof or combinations with another polyisocyanate.

4. The non-elastomeric biomedical adhesive composition according to claim 1, wherein said polyol is polyester glycol containing between 25 and 55 carbon atoms.

5. The non-elastomeric biomedical adhesive composition according to claim 1, wherein said polyol is: sorbitan monolaurate, sorbitan monostearate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20)

sorbitan monooleate, sorbitan mono-9-octo-decenoate, lauryl gallate or any mixture thereof.

6. The non-elastomeric biomedical adhesive composition according to claim 1, wherein an additional polyol may be incorporated being selected from the group consisting of: glycerol, ethylene glycol, polyethylene glycol, polypropylene glycol, poly-tetrahydrofuran, polycaprolactone diol, glycerol monostearate and polycaprolactone triol.

7. The non-elastomeric biomedical adhesive composition according to claim 1, wherein said compounds of calcium and phosphorus, are selected from tricalcium phosphate, hydroxyapatite, calcium salt of phosphorglyceric acid, glucose-6-calcium salt of phosphoric acid and glucose-1-calcium salt of phosphoric acid.

8. The non-elastomeric biomedical adhesive composition according to claim 2, wherein the optional catalyst to be used is selected from: sodium trichlorophenate, sodium tetrachlorophenate, sodium pentachlorophenate, ferric 2-ethylhexanoate, ferric acetylacetonate, dibutyltin-di-2-ethylhexanoate,stannous- 2-ethylhexanoate and cobalt 2-ethylhexanoate.

9. The non-elastomeric biomedical adhesive composition according to claim 1, wherein an inert filler is incorpoted.

10. The non-elastomeric biomedical adhesive composition according to claim 9, wherein said inert filler is selected from carbon black, metal oxides, stabilizers, ceramic powders, acrylic and methacrylic resin powders, and plasticizers.

* * * * *

Exhibit 3

US005328687A

United States Patent [19]

Leung et al.

[11] Patent Number: 5,328,687

[45] Date of Patent: Jul. 12, 1994

[54] **BIOCOMPATIBLE MONOMER AND POLYMER COMPOSITIONS**

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[22] Filed: Mar. 31, 1993

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[58] Field of Search 424/423, 78.35, 451, 424/489; 526/297, 300, 341; 606/228; 514/963; 264/4.1, 4.3, 4.6

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[57] ABSTRACT

A biocompatible monomer composition contains (A) at least one monomer of the formula:

CHR=CXY

wherein X and Y are each strong electron withdrawing groups, and R is H or, provided that X and Y are both cyano groups, a C_1-C_4 alkyl group; and (B) an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels, preferably a formaldehyde scavenger compound. The monomer is preferably an alpha-cyanoacrylate. The formaldehyde scavenger compound may be in microencapsulated or non-microencapsulated form. The composition can be applied to a variety of materials and is particularly suitable as in vivo tissue adhesive. A method of joining together in vivo two surfaces, e.g., body tissues, includes (a) applying to at least one of the surfaces a composition containing 1) at least one monomer, preferably an alpha-cyanoacrylate, which forms a polymer whose in vivo biodegradation produces formaldehyde; and 2) an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels, preferably a formaldehyde scavenger; and (b) maintaining the surfaces in contact until the composition polymerizes.

16 Claims, No Drawings

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BIOCOMPATIBLE MONOMER AND POLYMER COMPOSITIONS

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to monomer and poller compositions useful to form biomedical adhesives, sealants, bioactive agent release matrices, and implants. More particularly, this invention relates to biocompatible monomer and polymer compositions particularly useful for medical, surgical and other in vivo applications.

2. Related Developments

The products in primary use for wound closure are surgical sutures and staples. Sutures are recognized to provide adequate wound support. However, sutures cause additional trauma to the wound site (by reason of the need for the needle and suture to pass through tissue) and are time-consuming to place, and, at skin level, can cause unattractive wound closure marks. Surgical staples have been developed to speed wound apposition and provide improved cosmetic results. However, surgical staples also impose additional wound trauma and require the use of ancillary and often expensive devices for positioning and applying the staples.

To overcome these drawbacks, fast-acting surgical adhesives have been proposed. One group of such adhesives is the monomeric forms of alpha-cyanoacrylates.

Reference is made, for example, to U.S. Pat. Nos. 3,527,841 (Wicker et al.); 3,722,599 (Robertson et al.); 3,995,641 (Kronenthal et al.); and 3,940,362 (Overhults), which disclose that alpha-cyanoacrylates are useful as surgical adhesives. All of the foregoing references are hereby incorporated by reference herein.

Typically, when used as adhesives and sealants, cyanoacrylates are applied in monomeric form to the surfaces to be joined or sealed, where, typically, in situ anionic polymerization of the monomer occurs, giving rise to the desired adhesive bond or seal. Implants, such as rods, meshes, screws, and plates, may be formed of cyanoacrylate polymers, formed typically by radical-initiated polymerization.

However, a drawback to the in vivo biomedical use of alpha-cyanoacrylate monomers and polymers has been their potential for causing adverse tissue response. For example, methyl alpha-cyanoacrylate has been reported to cause tissue inflammation at the site of application.

The adverse tissue response to alpha-cyanoacrylates appears to be caused by the products released during in vivo biodegradation of the polymerized alpha-cyanoacrylates. It is believed that formaldehyde is the biodegradation product most responsible for the adverse tissue response and, specifically, the high concentration of formaldehyde produced during rapid polymer biodegradation. Reference is made, for example, to F. Leonard et al., *Journal of Applied Polymer Science*, Vol. 10, pp. 259-272 (1966); F. Leonard, *Annals New York Academy of Sciences*, Vol. 146, pp. 203-213 (1968); Tseng, Yin-Chao, et al., *Journal of Applied Biomaterials*, Vol. 1, pp. 111-119 (1990), and to Tseng, Yin-Chao, et al., *Journal of Biomedical Materials Research*, Vol. 24, pp. 1355-1367 (1990), which are both hereby incorporated by reference herein.

For these reasons, cyanoacrylates have not come into widespread use for biomedical purposes.

Efforts to increase the tissue compatibility of alpha-cyanoacrylates have included modifying the alkyl ester group. For example, increasing the alkyl ester chain length to form the higher cyanoacrylate analogues, e.g., butyl-2-cyanoacrylates and octyl-2-cyanoacrylates, has been found to improve biocompatibility but the higher analogues biodegrade at slower rates than the lower alkyl cyanoacrylates.

Other examples of modified alpha-cyanoacrylates used in biomedical applications include carbalkoxyalkyl alpha-cyanoacrylates (see, for example, U.S. Pat. No. 3,995,641 to Kronenthal et al.), fluorocyanoacrylates (see, for example, U.S. Pat. No. 3,722,599 to Robertson et al.), and alkoxyalkyl 2-cyanoacrylates (see, for example, U.S. Pat. No. 3,559,652 to Banitt et al.). Other efforts have included mixing alpha-cyanoacrylates with dimethyl methylenemalonate and higher esters of 2-cyanoacrylic acid (see, for example, U.S. Pat. No. 3,591,676 to Hawkins et al.).

In other efforts to increase the usefulness of alpha-cyanoacrylate adhesive compositions for surgical applications, certain viscosity modifiers have been used in combination with alkyl alpha-cyanoacrylate monomers, such as methyl alpha-cyanoacrylate. See, for example, U.S. Pat. No. 3,564,078 (wherein the viscosity modifier is poly(ethyl 2-cyanoacrylate)) and U.S. Pat. No. 3,527,841 (wherein the viscosity modifier is poly(lactic acid)), both patents being to Wicker et al.

Techniques for suppressing formaldehyde in industrial processes utilizing synthetic polymeric resins are known. However, the concept of suppressing formaldehyde as a mechanism for improving biocompatibility of polymers that biodegrade in vivo has not been suggested.

SUMMARY OF THE INVENTION

The present invention is based on the discovery that combining the monomers described hereinafter, and particularly the alpha-cyanoacrylate monomer(s), with a biocompatible agent effective to reduce active formaldehyde concentration levels, preferably a formaldehyde scavenger, which may be either in microencapsulated form or in non-microencapsulated form, will substantially improve the biocompatibility of polymers formed from such monomers. Furthermore, the present invention increases the biocompatibility of lower alkyl alpha-cyanoacrylate monomers and polymers and therefore increases the effectiveness of such monomers and polymers in in vivo applications.

Accordingly, one embodiment of the present invention provides a biocompatible monomer composition, comprising:

A) at least one monomer of the formula:

(I)

X and Y are each strong electron withdrawing groups, and R is H, or, provided that X and Y are both cyano groups, a C_1-C_4 alkyl group; and

B) an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

In another embodiment, the present invention is directed to a biocompatible composition comprising A) at least one copolymer of two monomers of formula (I) or one monomer of formula (I) and a monomer having the formula:

(II)

wherein X and Y are as defined above and Z is $-CH=CH_2$ and component B) described above.

In a further embodiment, the present invention is directed to a biocompatible composition comprising A) a polymer whose in vivo biodegradation produces formaldehyde and component B) described above.

In other embodiments, the present invention is directed to methods of using the above-described monomers, copolymers and polymers made therefrom for biomedical purposes.

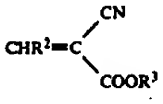
Preferably, the monomer is an alpha-cyanoacrylate. The monomer compositions of this invention and polymers formed therefrom are useful as tissue adhesives, sealants for preventing bleeding or for covering open wounds, systems for delivery of therapeutic or other bioactive agents, and in other biomedical applications. They find uses in, for example, apposing surgically incised or traumatically lacerated tissues; setting fractured bone structures; retarding blood flow from wounds; aiding repair and regrowth of living tissue; as matrices for delivering bioactive agents and as implants.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The monomers of formula (I) used in this invention are polymerizable, e.g. anionically polymerizable or free radical polymerizable, to form polymers which biodegrade to form active formaldehyde. As used herein, the language "active formaldehyde" refers to formaldehyde which is active so as to cause adverse tissue response.

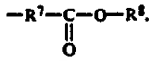
Examples of monomers within the scope of formula (I) include alpha-cyanoacrylates, vinylidene cyanides, C_1–C_4 alkyl homologues of vinylidene cyanides, dialkyl methylene malonates, acylacrylonitriles, vinyl sulfinates and vinyl sulfonates of the formula $CH_2=CX'Y'$ wherein X' is $-SO_2R'$ or $-SO_3R'$ and Y' is —CN, —COOR', $-COCH_3$, $-SO_2R'$ or $-SO_3R'$ and R' is H or hydrocarbyl.

Preferred monomers of formula (I) for use in this invention are alpha-cyanoacrylates. These monomers are known in the art and have the formula

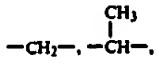


(III)

wherein R^2 is hydrogen and R^3 is a hydrocarbyl or substituted hydrocarbyl group; a group having the formula $-R^4-O-R^5-O-R^6$, wherein R^4 is a 1,2-alkylene group having 2–4 carbon atoms, R^5 is an alkylene group having 2–4 carbon atoms, and R^6 is an alkyl group having 1–6 carbon atoms; or a group having the formula



wherein R^7 is



or $-C(CH_3)_2-$ and R^8 is an organic radical.

Examples of suitable hydrocarbyl and substituted hydrocarbyl groups include straight chain or branched chain alkyl groups having 1–16 carbon atoms; straight chain or branched chain C_1–C_{16} alkyl groups substituted with an acyloxy group, a haloalkyl group, an alkoxy group, a halogen atom, a cyano group, or a haloalkyl group; straight chain or branched chain alkenyl groups having 2 to 16 carbon atoms; straight chain or branched chain alkynyl groups having 2 to 12 carbon atoms; cycloalkyl groups; aralkyl groups; alkylaryl groups; and aryl groups.

In the cyanoacrylate monomer of formula (III), R^3 is preferably an alkyl group having 1–10 carbon atoms or a group having the formula $-AOR^9$, wherein A is a divalent straight or branched chain alkylene or oxyalkylene radical having 2–8 carbon atoms, and R^9 is a straight or branched alkyl radical having 1–8 carbon atoms.

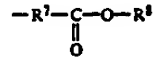
Examples of groups represented by the formula $-AOR^9$ include 1-methoxy-2-propyl, 2-butoxy ethyl, isopropoxy ethyl, 2-methoxy ethyl, and 2-ethoxy ethyl.

The most preferred alpha-cyanoacrylate monomers used in this invention are methyl alpha-cyanoacrylate, butyl alpha-cyanoacrylate, octyl alpha-cyanoacrylate, 1-methoxy-2-propyl cyanoacrylate, 2-butoxy ethyl cyanoacrylate, and isopropoxy-ethyl cyanoacrylate.

The alpha-cyanoacrylates of formula (III) wherein R^3 is a hydrocarbyl or substituted hydrocarbyl group can be prepared according to methods known in the art. Reference is made, for example, to U.S. Pat. Nos. 2,721,858 and 3,254,111, each of which is hereby incorporated by reference herein. For example, the alpha cyanoacrylates can be prepared by reacting an alkyl cyanoacetate with formaldehyde in a non-aqueous organic solvent and in the presence of a basic catalyst, followed by pyrolysis of the anhydrous intermediate polymer in the presence of a polymerization inhibitor. The alpha-cyanoacrylate monomers prepared with low moisture content and essentially free of impurities are preferred for biomedical use.

The alpha-cyanoacrylates of formula (III) wherein R^3 is a group having the formula $-R^4-O-R^5-O-R^6$ can be prepared according to the method disclosed in U.S. Pat. No. 4,364,876 (Kimura et al.), which is hereby incorporated by reference herein. In the Kimura et al. method, the alpha-cyanoacrylates are prepared by producing a cyanoacetate by esterifying cyanoacetic acid with an alcohol or by transesterifying an alkyl cyanoacetate and an alcohol; condensing the cyanoacetate and formaldehyde or para-formaldehyde in the presence of a catalyst at a molar ratio of 0.5–1.5:1, preferably 0.8–1.2:1, to obtain a condensate; depolymerizing the condensation reaction mixture either directly or after removal of the condensation catalyst to yield crude cyanoacrylate; and distilling the crude cyanoacrylate to form a high purity cyanoacrylate.

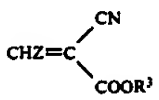
The alpha-cyanoacrylates of formula (III) wherein R^3 is a group having the formula



can be prepared according to the procedure described in U.S. Pat. No. 3,995,641 (Kronenthal et al.), which is hereby incorporated by reference herein. In the Kronenthal et al. method, such alpha-cyanoacrylate monomers are prepared by reacting an alkyl ester of an alpha-cyanoacrylic acid with a cyclic 1,3-diene to form a

Dieis-Alder adduct which is then subjected to alkaline hydrolysis followed by acidification to form the corresponding alpha-cyanoacrylic acid adduct. The alpha-cyanoacrylic acid adduct is preferably esterified by an alkyl bromoacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct. Alternatively, the alpha-cyanoacrylic acid adduct may be converted to the alpha-cyanoacrylyl halide adduct by reaction with thionyl chloride. The alpha-cyanoacrylyl halide adduct is then reacted with an alkyl hydroxyacetate or a methyl substituted alkyl hydroxyacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct or carbalkoxy alkyl alpha-cyanoacrylate adduct, respectively. The cyclic 1,3-diene blocking group is finally removed and the carbalkoxy methyl alpha-cyanoacrylate adduct or the carbalkoxy alkyl alpha-cyanoacrylate adduct is converted into the corresponding carbalkoxy alkyl alpha-cyanoacrylate by heating the adduct in the presence of a slight deficit of maleic anhydride.

Examples of monomers of formula (II) include cyanopentadienoates and alpha-cyanoacrylates of the formula:



(IV)

wherein Z is $-CH=CH_2$ and R^3 is as defined above. The monomers of formula (IV) wherein R^3 is an alkyl group of 1-10 carbon atoms, i.e., the 2-cyanopenta-2,4-dienoic acid esters, can be prepared by reacting an appropriate 2-cyanoacetate with acrolein in the presence of a catalyst such as zinc chloride. This method of preparing 2-cyanopenta-2,4-dienoic acid esters is disclosed, for example, in U.S. Pat. No. 3,554,990, which is hereby incorporated by reference herein.

Component B) of the compositions of this invention is at least one biocompatible agent effective to reduce active formaldehyde concentration levels (also referred to herein as "formaldehyde concentration reducing agents"). Preferably, component B) is a formaldehyde scavenger compound. Examples of formaldehyde scavenger compounds useful in this invention include sulfites; bisulfites; mixtures of sulfites and bisulfites; ammonium sulfite salts; amines; amides; imides; nitriles; carbamates; alcohols; mercaptans; proteins; mixtures of amines, amides, and proteins; active methylene compounds such as cyclic ketones and compounds having a β-dicarbonyl group; and heterocyclic ring compounds free of a carbonyl group and containing an NH group, with the ring made up of nitrogen or carbon atoms, the ring being unsaturated or, when fused to a phenyl group, being unsaturated or saturated, and the NH group being bonded to a carbon or a nitrogen atom, which atom is directly bonded by a double bond to another carbon or nitrogen atom.

Bisulfites and sulfites useful as the formaldehyde scavenger compound in this invention include alkali metal salts such as lithium, sodium and potassium salts, and ammonium salts, for example, sodium bisulfite, potassium bisulfite, lithium bisulfite, ammonium bisulfite, sodium sulfite, potassium sulfite, lithium sulfite, ammonium sulfite, and the like.

Examples of amines useful in this invention include the aliphatic and aromatic amines such as, for example, aniline, benzidine, aminopyrimidine, toluene-diamine, triethylenediamine, diphenylamine, diaminodiphenylamine, hydrazines and hydrazide.

Suitable proteins include collagen, gelatin, casein, soyabean protein, vegetable protein, keratin and glue. The preferred protein for use in this invention is casein.

Suitable amides for use in this invention include urea, cyanamide, acrylamide, benzamide, and acetamide. Urea is the preferred amide.

Suitable alcohols include phenols, 1,4-butanediol, d-sorbitol, and polyvinyl alcohol.

Examples of suitable compounds having a β-dicarbonyl group include malonic acid, acetylacetone, ethylacetone, acetate, malonamide, diethylmalonate or another malonic ester.

Preferred cyclic ketones for use in this invention include cyclohexanone or cyclopentanone.

Examples of suitable heterocyclic compounds for use as the formaldehyde scavenger in this invention are disclosed, for example, in U.S. Pat. No. 4,127,382 (Perry) which is hereby incorporated by reference herein. Such heterocyclic compounds include, for example, benzimidazole, 5-methyl benzimidazole, 2-methylbenzimidazole, indole, pyrrole, 1,2,4-triazole, indoline, benzotriazole, indoline, and the like.

The preferred formaldehyde scavenger for use in this invention is sodium bisulfite.

In practicing this invention, the formaldehyde concentration reducing agent, e.g., formaldehyde scavenger compound, is added in an effective amount to the cyanoacrylate. The "effective amount" is that amount sufficient to reduce the amount of formaldehyde generated during subsequent in vivo biodegradation of the polymerized cyanoacrylate. This amount will depend on the type of active formaldehyde concentration reducing agent, and can be readily determined without undue experimentation by those skilled in the art.

The formaldehyde concentration reducing agent may be used in this invention in either free form or in microencapsulated form.

When microencapsulated, the formaldehyde concentration reducing agent is released from the microcapsule continuously over a period of time during the in vivo biodegradation of the cyanoacrylate polymer.

For purposes of this invention, the microencapsulated form of the formaldehyde concentration reducing agent is preferred because this embodiment prevents or substantially reduces polymerization of the cyanoacrylate monomer by the formaldehyde concentration reducing agent, which increases shelf-life and facilitates handling of the monomer composition during use.

Microencapsulation of the formaldehyde scavenger can be achieved, by many known microencapsulation techniques. For example, microencapsulation can be carried out by dissolving a coating polymer in a volatile solvent, e.g., methylene chloride, to a polymer concentration of about 6% by weight; adding a formaldehyde scavenger compound in particulate form to the coating polymer/solvent solution under agitation to yield a scavenger concentration of 18% by weight; slowly adding a surfactant-containing mineral oil solution to the polymer solution under rapid agitation; allowing the volatile solvent to evaporate under agitation; removing the agitator; separating the solids from the mineral oil; and washing and drying the microparticles. The size of the microparticles will range from about 0.001 to about 1000 microns.

The coating polymer for microencapsulating the formaldehyde concentration reducing agent should be polymers which undergo in vivo bioerosion, preferably at rates similar to or greater than the cyanoacrylate polymer formed by the monomer, and should have low inherent moisture content. Such "bioerosion" can occur as a result of the physical or chemical breakdown of the encapsulating material, for example, by the encapsulating material passing from solid to solute in the presence of body fluids, or by biodegradation of the encapsulating material by agents present in the body.

Examples of coating materials which can be used to microencapsulate the formaldehyde concentration reducing agent include polyesters, such as polyglycolic acid, polylactic acid, copolymers of polyglycolic acid and polylactic acid, polycaprolactone, poly-β-hydroxybutyrate, copolymers of epsilon-caprolactone and delta-valerolactone, copolymers of epsilon-caprolactone and DL-dilactide, and polyester hydrogels; polyvinylpyrrolidone; polyamides; gelatin; albumin; proteins; collagen; poly(orthoesters); poly (anhydrides); poly (alkyl-2-cyanoacrylates); poly(dihydropyrans); poly(acetals); poly(phosphazenes); poly (urethanes); poly (dioxinones); cellulose; and starches.

Examples of the surfactant which can be added to the mineral oil include those commercially available under the designations Triton x-100, Tween 20 and Tween 80.

The composition of this invention may further contain a stabilizer and/or one or more adjuvant substances, such as thickening agents, plasticizers, or the like, to improve the medical utility of the monomer for particular medical applications.

Examples of suitable stabilizers include sulfur dioxide, sulfonic acid, lactone, boron trifluoride, hydroquinone, hydroquinone monomethyl ether, catechol, pyrogallol, benzoquinone, 2-hydroxybenzoquinone, p-methoxy phenol, t-butyl catechol, organic acid, butylated hydroxy anisole, butylated hydroxy toluene, t-butyl hydroquinone, alkyl sulfate, alkyl sulfite, 3-sulfolene, alkylsulfone, alkyl sulfoxide, mercaptan, and alkyl sulfide.

Suitable thickeners include, for example, polycyanoacrylates, polylactic acid, polyglycolic acid, lactic-glycolic acid copolymers, polycaprolactone, lactic acid-caprolactone copolymers, poly-3-hydroxybutyric acid, polyorthoesters, polyalkyl acrylates, copolymers of alkylacrylate and vinyl acetate, polyalkyl methacrylates, and copolymers of alkyl methacrylates and butadiene.

Examples of suitable plasticizers include dioctyl phthalate, dimethyl sebacate, triethyl phosphate, tri(2-ethylhexyl)phosphate, tri(p-cresyl) phosphate, glyceryl triacetate, glyceryl tributyrate, diethyl sebacate, dioctyl adipate, isopropyl myristate, butyl stearate, lauric acid, dibutyl phthalate, trioctyl trimellitate, and dioctyl glutarate.

To improve the cohesive strength of adhesives formed from the compositions of this invention, difunctional monomeric cross-linking agents may be added to the monomer compositions of this invention. Such crosslinking agents are known. Reference is made, for example, to U.S. Pat. No. 3,940,362 (Overhults), which is hereby incorporated by reference herein. Examples of suitable crosslinking agents include alkyl bis(2-cyanoacrylates), triallyl isocyanurates, alkylene diacrylates, alkylene dimethacrylates, trimethylol propane triacrylate, and alkyl bis(2-cyanoacrylates). A catalytic amount of an amine activated free radical initiator is added to initiate polymerization of the cyanoacrylate monomer/crosslinking agent blend. Such compositions can be molded or otherwise formed to provide preformed implants for surgical use, such as rods, meshes, plates, and screws.

The compositions of this invention may further contain fibrous reinforcement and colorants, i.e., dyes and pigments. Examples of suitable fibrous reinforcement include PGA microfibrils, collagen microfibrils, cellulosic microfibrils, and olefinic microfibrils. Examples of suitable colorants include 1-hydroxy-4-[4-methylphenylamino]-9,10 anthracenedione (D+C violet No. 2); disodium salt of 6-hydroxy-5-[(4-sulfophenyl)axo]-2-naphthalenesulfonic acid (FD+C Yellow No. 6); 9-(o-carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthen-3-one, disodium salt, monohydrate (FD+C Red No. 3); 2-(13-dihydro-3-oxo-5-sulfo-2H-indol-2-ylidene)-2,3-dihydro-3-oxo-1H-indole-5 -sulfonic acid disodium salt (FD+C Blue No. 2); and [phthalocyaninato (2-)] copper.

The compositions of this invention can be used to join together two surfaces by applying the particular composition to at least one of said surfaces. Depending on the particular requirements of the user, the adhesive compositions of this invention can be applied by known means such as with a glass stirring rod, sterile brush or medicine dropper; however, in many situations a pressurized aerosol dispensing package is preferred in which the adhesive composition is in solution with a compatible anhydrous propellant. Aerosol application of the monomers is particularly advantageous for use in hemostasis.

In one embodiment, the present invention is directed to a method of joining together in vivo two surfaces which comprises (a) applying to at least one of said surfaces a composition of this invention, e.g., a composition comprising 1) at least one monomer (e.g., a monomer of formula (I)) which forms a polymer whose in vivo biodegradation produces formaldehyde; and 2) an effective amount of a biocompatible agent effective to reduce active formaldehyde concentration levels, preferably a formaldehyde scavenger compound; and (b) maintaining the surfaces in contact until said composition polymerizes. One of said surfaces can be body tissue and the other surface a prosthetic device, or both surfaces may be body tissue.

In another embodiment, the present invention is directed to a method for effecting in vivo administration of a bioactive agent, comprising introducing into a body a composition comprising a polymer whose in vivo biodegradation produces formaldehyde, an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels, and a bioactive amount of a bioactive agent, wherein biodegradation of the polymer effects in vivo release of the bioactive agent. The bioactive agent may be encapsulated in a suitable biogradable material for controlling release of the bioactive agent.

Specific methods which may use a composition containing a monomer, the polymeric form of which produces formaldehyde upon in vivo biodegradation and an effective amount of a biocompatible agent effective to reduce active formaldehyde concentration levels, preferably a formaldehyde scavenger compound, include methods for repairing damaged living tissue to prevent the escape of fluids therethrough which comprises (a) applying to the tissue said monomer/formaldehyde concentration reducing agent composition;

and (b) allowing the composition to polymerize; methods for stemming the flow of blood from small vessels which comprises applying to said vessels a hemostatic agent comprising the monomer/formaldehyde concentration reducing agent composition; methods of dressing burns to promote the healing thereof which comprises (a) covering said burn with the monomer/formaldehyde concentration reducing agent composition; and (b) allowing the composition to polymerize; and methods of dressing wounds to promote the healing thereof which comprises (a) covering said wound with the monomer/formaldehyde concentration reducing agent composition; and (b) allowing the composition to polymerize.

Repairing injured tissues (for example, to control bleeding) comprises, in general, sponging to remove superficial body fluids and subsequent application to the exposed tissue of an adhesive composition containing a cyanoacrylate monomer. The composition polymerizes to a thin film of polymer while in contact with the tissue surface. Tissues which are not bleeding or otherwise covered by body fluids need not be sponged first. For bonding separate surfaces of body tissues, the monomer is applied to at least one surface, and the surfaces are brought quickly together while the monomer polymerizes in contact with both of the surfaces.

The compositions may further be used to administer therapeutic agents into the body. The composition will form a matrix for the therapeutic agent, with the therapeutic agent being released in vivo over time from the matrix during biodegradation of the polymer. Specifically, a composition comprising the monomer (or polymer form of the monomer, since in this particular application, polymerization need not occur in situ), a biocompatible agent effective to reduce active formaldehyde concentration levels, preferably a formaldehyde scavenger compound, and a therapeutic agent is introduced into the body where the polymer undergoes biodegradation, releasing the therapeutic agent.

The monomers are readily polymerized to addition-type polymers and copolymers, which are generally optically clear (as films).

In most bonding applications using the compositions of this invention, polymerization of the monomers is catalyzed by small amounts of moisture on the surface of the adherents; thus desired bonding of tissues or hemostasis proceeds well in the presence of blood and other body fluids. The bonds formed are of adequate flexibility and strength to withstand normal movement of tissue. In addition, bond strength is maintained as natural wound healing proceeds concurrently with polymer assimilation.

Compositions employed in the invention are sterilizable by conventional methods such as by autoclave or by aseptic filtration techniques.

The invention is further illustrated by the following non-limiting examples.

EXAMPLES

In the Examples below, the following terms are defined as follows:

MCA—methyl cyanoacrylate

IPECA—isopropoxyethyl cyanoacrylate

2-BECA—2-butoxy ethyl cyanoacrylate

MPCA—1-methoxy-2-propyl cyanoacrylate

monomer(s)—refers generically to MCA, IPECA, 2-BECA, and/or MPCA

EXAMPLES 1-12 AND CONTROL EXAMPLES A—C

Examples 1-12 and Control Examples A-C illustrate the effect of a formaldehyde scavenger on the amount of formaldehyde released during the biodegradation of a cyanoacrylate polymer. The compositions of Examples 1-12 each contain a formaldehyde scavenger while the compositions of Control Examples A-C do not.

The formulations of the compositions prepared in Examples 1-12 and Control Examples A-C are shown in Table I below.

The compositions of the examples are prepared as follows. The monomer and formaldehyde scavenger, in the appropriate weight ratio, are mixed thoroughly by shaking. (Solid formaldehyde scavengers are ground or milled to a fine particle size prior to mixing.) The resulting mixture is quickly poured over an aluminum mesh (½"×5" approximately) which is resting on a Teflon(R) sheet. The mesh is wetted to the fullest extent but not overflowed. Polymerization of the cyanoacrylate mixture is then accelerated by spraying with a 1% aqueous sodium bicarbonate solution. The hardened polymer supported by the aluminum mesh is gently scraped off from the Teflon(R) sheet, rinsed with water and dried.

In vitro biodegradation of the polymer films is then carried out as follows. The mesh-supported polymer film is placed in a PH 7.41 buffer solution (monobasic potassium phosphate and disodium phosphate). Biodegradation is carried out at 80°±2° C. for 75 hours. The partially degraded film is separated from the buffer solution, rinsed with water and dried. The buffer solution is centrifuged, and the clear solution thus obtained is then subjected to formaldehyde determination.

The amount of formaldehyde generated during biodegradation of the polymer films is determined by means of a spectrophotometric method using Nash's Reagent. This method is similar to Method 964.21 described in AOAC Official Methods of Analysis, 1990, Volume 2, p. 1037. In the following tables, the term "ug formaldehyde/mg polymer" means the amount of formaldehyde generated in micrograms divided by the original polymer weight in milligrams (excluding the weight of the scavenger).

The results are presented in Table I.

TABLE I

Examples 1-12 and Control Examples A-C: Formulations and Formaldehyde Generation

Example No.	Monomer	Formaldehyde Scavenger	Scavenger Weight %	µg Formaldehyde Detected Per mg Polymer	% Reduction of Formaldehyde Detected
1	MCA	1,4 butandediol	20	1.25	—*
2	MCA	diphenylamine	20	0.53	51
3	MCA	gelatin	20	1.04	5
4	MCA	casein	20	1.36	—*
A	MCA	None-Control for Ex. 1-4	0	1.09	0

TABLE I-continued

Examples 1-12 and Control Examples A-C: Formulations and Formaldehyde Generation

Example No.	Monomer	Formaldehyde Scavenger	Scavenger Weight %	µg Formaldehyde Detected Per mg Polymer	% Reduction of Formaldehyde Detected
5	IPECA	sodium bisulfite	20	<0.05	100
6	IPECA	urea	20	0.12	88
7	IPECA	casein	30	0.08	92
8	IPECA	polyvinyl alcohol	30	0.22	79
B	IPECA	None-Control for Ex. 5-8	0	1.03	0
9	IPECA	acrylamide	20	0.18	70
10	IPECA	D-sorbitol	20	0.25	58
11	IPECA	4-methoxyphenol	20	0.44	27
12	IPECA	1,3-dihydroxy-2-propanone	20	0.44	27
C	IPECA	None-Control for Ex. 9-12	0	0.60	0

*No reduction detected. The reason that the amount of formaldehyde detected in these samples is greater than the control is believed to result from the fact that the MCA/scavenger composition degraded faster than the control. with a 75-79% weight loss of the MCA/scavenger compositions compared with approximately a 50% weight loss of the control.

The results set forth in Table I show that a significant reduction of formaldehyde generation occurs during polymer biodegradation when a formaldehyde scavenger is present.

EXAMPLES 13-20 AND CONTROL EXAMPLES D-G

Examples 13-20 and Control Examples D-G illustrate the effect of a microencapsulated formaldehyde scavenger on the amount of formaldehyde generated during cyanoacrylate polymer biodegradation. The compositions of Examples 13-20 contain microencapsulated formaldehyde scavengers while the compositions of the Control Examples do not contain any formaldehyde scavenger.

The formulations of the compositions prepared in Examples 13-20 and Control Examples D-G are shown in Table II below.

The compositions of these examples are prepared in the same manner as are the compositions in Examples 1-12 and Control Examples A-C, except that the formaldehyde scavenger is used in microencapsulated form. Microencapsulation of the scavenger is carried out as follows. In a 500 ml resin kettle, a coating polymer (e.g., polyglycolic-colactic acid, polyvinylpyrrol idone, or polycaprolactone) is dissolved in a volatile solvent, e.g., methylene chloride. The final concentration is approximately 6% (w/v). The particulate scavenger (e.g., sodium bisulfite, urea, casein, or polyvinyl alcohol) is then added to the solution under agitation. Its concentration with respect to the solution volume is approximately 18%. In a separate container, a 1% surfactant (e.g., Triton x-100, Tween 20, or Tween 80) in mineral oil is prepared. Under rapid agitation, the mineral oil solution is slowly added to the polymer solution. The volatile solvent is allowed to evaporate under agitation. This typically is allowed to proceed for 12-20 hours under ambient conditions. At the end of this period, the agitator is removed and the solids are separated from the mineral oil. The particles are washed in hexane 3-4 times and dried. The resulting particles range in size from 10-1000 microns.

In vitro degradation of the polymer films and formaldehyde determination are carried out using the same procedures followed in Examples 1-12 and Control Examples A-C. The results are shown in Table II.

TABLE II

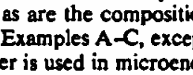
Examples 13-20 and Control Examples D-G: Formulations and Formaldehyde Generation

Example No.	Monomer	Microcapsule Coating/Scavenger	Microcapsule Weight %	µg Formaldehyde Detected Per mg Polymer	% Reduction of Formaldehyde Detected
13	MCA	50:50 PGA/PLA/Casein	20	2.0	57
14	MPCA	50:50 PGA/PLA/Sodium Bisulfite	20	0.2	97
15	MPCA	Polyvinyl Pyrrolidone/Urea	20	0.9	84
16	MPCA	50:50 PGA/PLA/Casein	20	2.2	62
17	2-BECA	50:50 PGA/PLA/Sodium Bisulfite	20	<0.1	100
18	2-BECA	Polyvinyl Pyrrolidone/Urea	20	1.4	67
19	IPECA	Polycaprolactone/Polyvinyl Alcohol	20	2.5	26
20	IPECA	Polyvinyl Pyrrolidone/Urea	20	1.1	68
D	MCA	None	0	4.7	0
E	MPCA	None	0	5.8	0
F	2-BECA	None	0	4.2	0
G	IPECA	None	0	3.4	0

What is claimed is:

1. A biocompatible monomer composition, comprising:

A. at least one monomer of the formula:



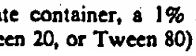
(I)

wherein X and Y are each strong electron withdrawing groups, and R is H or, provided that X and Y are both cyano groups, a C_1-C_4 alkyl group; and

B. an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

2. A biocompatible monomer composition, comprising:

A. at least one monomer of the formula:



(I)

X and Y are each strong electron withdrawing groups, and R is H or, provided that X and Y are both cyano groups, a C_1–C_4 alkyl group; and

B. an effective amount of at least one formaldehyde scavenger compound.

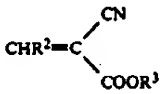
3. A composition according to claim 1, wherein the at least one monomer is anionically polymerizable.

4. A composition according to claim 1, wherein the at least one monomer is free radical polymerizable.

5. A composition according to claim 1, wherein the at least one monomer is an alpha-cyanoacrylate, a vinylidene cyanide, a C_1–C_4 alkyl homolog of a vinylidene cyanide, a dialkyl methylene malonate, an acylacrylonitrile, a vinyl sulfinate or vinyl sulfonate of the formula $CH_2{=}CX'Y'$ where X' is $-SO_2R'$ or $-SO_3R'$ and Y' is $-CN$, $-COOR'$, $-COCH_3$, $-SO_2R'$ or $-SO_3R'$, and R' is H or hydrocarbyl.

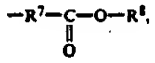
6. A composition according to claim 5, wherein the at least one monomer is an alpha-cyanoacrylate.

7. A composition according to claim 6, wherein the alpha-cyanoacrylate monomer has the formula

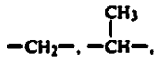


(III)

wherein R^2 is hydrogen and R^3 is a hydrocarbyl or substituted hydrocarbyl group; a group having the formula $-R^4-O-R^5-O-R^6$ wherein is a 1,2-alkylene group having 2–4 carbon atoms, R^5 is an alkylene group having 2–4 carbon atoms, and R^6 is an alkyl group having 1–6 carbon atoms; or a group having the formula



wherein R^7 is



or $-C(CH_3)_2-$ and R^8 is an organic radical.

8. A composition according to claim 7, wherein R^3 is a hydrocarbyl or substituted hydrocarbyl group, selected from the group consisting of straight chain or branched chain alkyl groups having 1–16 carbon atoms; straight chain or branched chain C_{1-16} alkyl groups substituted with an acyloxy group, a haloalkyl group, an alkoxy group, a halogen atom, a cyano group, or a haloalkyl group; straight chain or branched chain alkenyl groups having 2 to 16 carbon atoms; straight chain or branched chain alkynyl groups having 2 to 12 carbon atoms; cycloalkyl groups; aralkyl groups; alkylaryl groups; and aryl groups.

9. A composition according to claim 8, wherein R^3 is an alkyl group having 1–6 carbon atoms or a group having the formula $-AOR^9$ wherein A is a divalent straight or branched chain alkylene or oxyalkylene radical having 2–8 carbon atoms, and R^9 is a straight or branched alkyl radical having 1–8 carbon atoms.

10. A composition according to claim 9, wherein the alpha-cyanoacrylate is methyl cyanoacrylate, butyl cyanoacrylate, octyl cyanoacrylate, 1-methoxy-2-propyl cyanoacrylate, 2-butoxy ethyl cyanoacrylate, or isopropoxy-ethyl cyanoacrylate.

11. A composition according to claim 2, wherein the at least one formaldehyde scavenger compound is sodium bisulfite.

12. A composition according to claim 2, wherein the at least one biocompatible agent effective to reduce active formaldehyde concentration levels is in microencapsulated form.

13. A composition according to claim 1, wherein the at least one biocompatible agent effective to reduce active formaldehyde concentration levels is microencapsulated with a coating polymer which undergoes in vivo bioerosion and which has a low inherent moisture content.

14. A composition according to claim 13, wherein the at least one biocompatible agent effective to reduce active formaldehyde concentration levels is microencapsulated with a coating material selected from the group consisting of polyglycolic acid, polylactic acid, copolymers of polyglycolic acid and polylactic acid, polycaprolactone, poly-β-hydroxybutyrate, copolymers of epsilon-caprolactone and delta-valerolactone, copolymers of epsilon-caprolactone and DL-dilactide, polyester hydrogels, polyvinylpyrrolidone, polyamides, gelatin, albumin, proteins, collagen, poly(orthoesters), poly(anhydrides) poly(alkyl-2-cyanoacrylates), poly(dihydropyrans), poly(acetals), poly(phosphazenes), poly(urethanes), poly(dioxinones), cellulose, and starches.

15. A biocompatible composition comprising A) at least one copolymer of two monomers each having the formula:

$$CHR{=}CXY \qquad (I)$$

wherein X and Y are each strong electron withdrawing groups, and R is H or, provided that X and Y are both cyano groups, a C_1–C_4 alkyl group or at least one copolymer of a monomer of formula (I) and a monomer having the formula:

$$CHZ{=}CXY \qquad (II)$$

wherein X and Y are as defined above and Z is $-CH{=}CH_2$ and

B. an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

16. A biocompatible composition, comprising

A. a polymer whose in vivo biodegradation produces formaldehyde and

B. an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels, wherein the polymer is a polymerized form of (a) at least one monomer of the formula:

$$CHR{=}CXY \qquad (I)$$

wherein X and Y are each strong electron withdrawing groups, and R is H or, provided that X and Y are both cyano groups, a C_1–C_4 alkyl group, or (b) at least one copolymer of two monomers each having the formula:

$$CHR{=}CXY \qquad (I)$$

wherein X and Y are each strong electron withdrawing groups, and R is H or, provided that X and Y are both cyano groups, a C_1–C_4 alkyl group or at least one copolymer of a monomer of formula (I) and a monomer having the formula:

$$CHZ=CXY \quad (II)$$

wherein X and Y are as defined above and Z is $-CH=CH_2$.

* * * * *

Exhibit 4

US006306243B1

(12) United States Patent
Clark et al.

(10) Patent No.: US 6,306,243 B1
(45) Date of Patent: *Oct. 23, 2001

(54) **PH-MODIFIED BIOCOMPATIBLE MONOMER AND POLYMER COMPOSITIONS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/588,621**

(22) Filed: **Jun. 7, 2000**

Related U.S. Application Data

(63) Continuation of application No. 08/714,288, filed on Sep. 18, 1996, now Pat. No. 6,143,352, which is a continuation of application No. 08/266,647, filed on Jun. 28, 1994, now abandoned.

(51) **Int. Cl.**[7] **C09J 101/00**

(52) **U.S. Cl.** **156/331.2**; 424/78.06; 424/78.55; 427/2.1; 523/118; 523/202; 523/205; 523/210; 526/298

(58) **Field of Search** 156/331.2; 427/2.1; 526/298; 523/118, 202, 205, 210; 424/78.35, 78.06, 487; 604/214

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(57) **ABSTRACT**

The pH-modified monomer and polymer compositions are useful as biomedical and surgical adhesives, sealants, implants and bioactive agent release carriers or matrices. They comprise a monomer or polymer; and an effective amount of an acidic or basic pH modifier effective to modify the pH of an immediate in vivo environment of the composition to a pH range at which the polymer biodegrades at a different rate than at physiologic pH. The invention also relates to in vivo applications in which surfaces are joined or treated with such pH-modified biocompatible compositions.

30 Claims, No Drawings

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PH-MODIFIED BIOCOMPATIBLE MONOMER AND POLYMER COMPOSITIONS

This application is a continuation of Ser. No. 08/714,288 filed Sep. 18, 1996, now U.S. Pat. No. 6,143,352 which is a continuation of Ser. No. 08/266,647 filed Jun. 28, 1994, abandoned.

FIELD OF THE INVENTION

This invention relates to improved compositions useful as biomedical adhesives, sealants, implants and bioactive agent release matrices. This invention also relates to medical, surgical and other in vivo applications in which body tissue surfaces are joined or reinforced with biocompatible compositions.

BACKGROUND

The products in primary use for wound closure are surgical sutures and staples. Sutures are recognized to provide adequate wound support. However, sutures cause additional trauma to the wound site (by reason of the need for the needle and suture to pass through tissue) and are time-consuming to place, and, at skin level, can cause unattractive wound closure marks. Surgical staples have been developed to speed wound apposition. However, surgical staples also impose additional wound trauma and require the use of ancillary and often expensive devices for positioning and applying the staples.

To overcome these drawbacks, fast-acting surgical adhesives have been proposed. One group of such adhesives is the monomeric forms of alpha-cyanoacrylates.

Reference is made, for example, to U.S. Pat. No. 3,527,841 (Wicker et al.); U.S. Pat. No. 3,722,599 (Robertson et al.); U.S. Pat. No. 3,995,641 (Kronenthal et al.); and U.S. Pat. No. 3,940,362 (Over-hults), which disclose that alpha-cyanoacrylates are useful as surgical adhesives. All of the foregoing references are hereby incorporated by reference herein.

Typically, when used as adhesives and sealants, cyanoacrylates are applied in monomeric form to the surfaces to be joined or sealed, where, typically, in situ anionic polymerization of the monomer occurs, giving rise to the desired adhesive bond or seal. Implants, such as rods, meshes, screws, and plates, may also be formed of cyanoacrylate polymers, formed typically by radical-initiated polymerization.

However, a drawback to the in vivo biomedical use of alpha-cyanoacrylate monomers and polymers has been their potential for causing adverse tissue response. For example, methyl alpha-cyanoacrylate has been reported to cause tissue inflammation at the site of application.

The adverse tissue response to alpha-cyanoacrylates appears to be caused by the products released during in vivo biodegradation of the polymerized alpha-cyanoacrylates. It is believed that formaldehyde is the biodegradation product most responsible for the adverse tissue response and, specifically, the high concentration of formaldehyde produced during rapid polymer biodegradation. Reference is made, for example, to F. Leonard et al., *Journal of Applied Polymer Science*, Vol. 10, pp. 259–272 (1966); F. Leonard, *Annals New York Academy of Sciences*, Vol. 146, pp. 203–213 (1968); Tseng, Yin-Chao, et al., *Journal of Applied Biomaterials*, Vol. 1, pp. 111–119 (1990), and to Tseng, Yin-Chao, et al., *Journal of Biomedical Materials Research*, Vol. 24, pp. 1355–1367 (1990).

For these reasons, cyanoacrylates have not come into widespread use for biomedical purposes.

Efforts to increase the tissue compatibility of alpha-cyanoacrylates have included modifying the alkyl ester group. For example, increasing the alkyl ester chain length to form the higher cyanoacrylate analogues, e.g., butyl-2-cyanoacrylates and octyl-2-cyanoacrylates, has been found to improve biocompatibility but the higher analogues biodegrade at slower rates than the lower alkyl cyanoacrylates.

Other examples of modified alpha-cyanoacrylates used in biomedical applications include carbalkoxyalkyl alpha-cyanoacrylates (see, for example, U.S. Pat. No. 3,995,641 to Kronenthal et al.), fluorocyanoacrylates (see, for example, U.S. Pat. No. 3,722,599 to Robertson et al.), and alkoxyalkyl 2-cyanoacrylates (see, for example, U.S. Pat. No. 3,559,652 to Banitt et al.). Other efforts have included mixing alpha-cyanoacrylates with dimethyl methylenemalonate and higher esters of 2-cyanoacrylic acid (see, for example, U.S. Pat. No. 3,591,676 to Hawkins et al.).

In other efforts to increase the usefulness of alpha-cyanoacrylate adhesive compositions for surgical applications, certain viscosity modifiers have been used in combination with alkyl alpha-cyanoacrylate monomers, such as methyl alpha-cyanoacrylate. See, for example, U.S. Pat. No. 3,564,078 (wherein the viscosity modifier is poly (ethyl 2-cyanoacrylate)) and U.S. Pat. No. 3,527,841 (wherein the viscosity modifier is poly(lactic acid)), both patents being to Wicker et al.

In a related application, U.S. Ser. No. 08/040,618, filed Mar. 31, 1993 (U.S. Pat. No. 5,328,687), the entire contents of which are hereby incorporated by reference, the use of formaldehyde scavengers has been proposed to improve biocompatibility of alpha-cyanoacrylate polymers, whose biodegradation produces formaldehyde, for use in in vivo applications. It is known that various compounds can affect polymerization of alpha-cyanoacrylate monomers, including acids to inhibit or slow polymerization (e.g., Leonard et al., U.S. Pat. No. 3,896,077), and bases to accelerate polymerization (e.g., Coover et al., U.S. Pat. No. 3,759,264 and Dombroski et al., U.S. Pat. No. 4,042,442).

SUMMARY OF THE INVENTION

It has not been known to regulate polymer biodegradation by regulating the pH of an immediate in vivo environment of a biocompatible composition. Such regulation would improve, for instance, the biocompatibility of 1,1-disubstituted ethylene polymers for in vivo applications, by controlling the rate of release of harmful byproducts (e.g., formaldehyde) and controlling the rate of degradation of the polymer in situ.

Combining the monomer composition with a biocompatible pH modifier effective to regulate the pH of an immediate environment of the in situ polymer will substantially improve the usefulness of polymers formed from such monomers, particularly in combination with use of formaldehyde scavengers.

The present invention is also directed to methods of using the above-described monomers, copolymers and polymers made therefrom for biomedical purposes.

The monomer compositions of this invention and polymers formed therefrom are useful as tissue adhesives, sealants for preventing bleeding or for covering open wounds, systems for delivery of therapeutic or other bioactive agents, and in other biomedical applications. They find uses in, for example, apposing surgically incised or traumatically lacerated tissues; setting fractured bone structures; retarding

blood flow from wounds; aiding repair and regrowth of living tissue; and serving as matrices for delivering bioactive agents and as implants.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Embodiments of the present invention provide a biocompatible monomer composition, comprising an effective amount of at least one biocompatible pH modifier effective to regulate the pH of an immediate in vivo environment of the polymer to a pH range at which the polymer's in vivo biodegradation proceeds at a different rate than it does at physiologic pH.

In a further embodiment, the present invention is directed to a biocompatible composition comprising a polymer whose in vivo biodegradation may produce formaldehyde, and a pH modifier as described previously, and optionally including a formaldehyde scavenger.

The monomers used in this invention are polymerizable, e.g. anionically polymerizable or free radical polymerizable, to form polymers which biodegrade. In some embodiments, they form active formaldehyde upon biodegradation.

Monomer compositions of this invention may be applied to a surface to be sealed or joined together with a second surface in vivo, where, typically, in situ anionic polymerization of the monomer occurs, giving rise to the desired adhesive bond or seal.

Useful 1,1-disubstituted ethylene monomers include, but are not limited to, monomers of the formula:

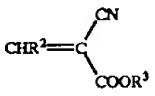
$$CHR{=}CXY \qquad (I)$$

wherein X and Y are each strong electron withdrawing groups, and R is H, $-CH{=}CH_2$ or, provided that X and Y are both cyano groups, a C_1–C_4 alkyl group.

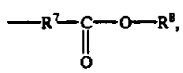
Examples of monomers within the scope of formula (I) include alpha-cyanoacrylates, vinylidene cyanides, C_1–C_4 alkyl homologues of vinylidene cyanides, dialkyl 2-methylene malonates, acylacrylonitriles, vinyl sulfinates and vinyl sulfonates of the formula $CH_2{=}CX'Y'$ wherein X' is $-SO_2R'$ or $-SO_3R'$ and Y' is —CN, —COOR', $-COCH_3$, $-SO_2R'$ or $-SO_3R'$, and R' is H or hydrocarbyl.

Preferred monomers of formula (I) for use in this invention are alpha-cyanoacrylates. These monomers are known in the art and have the formula

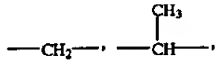
(II)



wherein R^2 is hydrogen and R^3 is a hydrocarbyl or substituted hydrocarbyl group; a group having the formula $-R^4-O-R^5-O-R^6$, wherein R^4 is a 1,2-alkylene group having 2–4 carbon atoms, R^5 is an alkylene group having 2–4 carbon atoms, and R^6 is an alkyl group having 1–6 carbon atoms; or a group having the formula



wherein R^7 is



or $-C(CH_3)_2-$, and R^8 is an organic radical.

Examples of suitable hydrocarbyl and substituted hydrocarbyl groups include straight chain or branched chain alkyl groups having 1–16 carbon atoms; straight chain or branched chain C_1–C_{16} alkyl groups substituted with an acyloxy group, a haloalkyl group, an alkoxy group, a halogen atom, a cyano group, or a haloalkyl group; straight chain or branched chain alkenyl groups having 2 to 16 carbon atoms; straight chain or branched chain alkynyl groups having 2 to 12 carbon atoms; cycloalkyl groups; aralkyl groups; alkylaryl groups; and aryl groups.

In the cyanoacrylate monomer of formula (II), R^3 is preferably an alkyl group having 1–10 carbon atoms or a group having the formula $-AOR^9$, wherein A is a divalent straight or branched chain alkylene or oxyalkylene radical having 2–8 carbon atoms, and R^9 is a straight or branched alkyl radical having 1–8 carbon atoms.

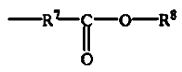
Examples of groups represented by the formula $-AOR^9$ include 1-methoxy-2-propyl, 2-butoxyethyl, 2-isopropoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxybutyl.

Especially advantageous alpha-cyanoacrylate monomers for use in this invention are methyl alphacyanoacrylate, butyl alpha-cyanoacrylate, 2-octyl alphacyanoacrylate, 1-methoxy-2-propyl cyanoacrylate, 2-butoxyethyl cyanoacrylate, 2-isopropoxyethyl cyanoacrylate and 3-methoxybutyl cyanoacrylate. Equally advantageous are 2-methylene malonates, such as dimethyl 2-methylenemalonate.

The alpha-cyanoacrylates of formula (II) wherein R^3 is a hydrocarbyl or substituted hydrocarbyl group can be prepared according to methods known in the art. Reference is made, for example, to U.S. Pat. No. 2,721,858 and U.S. Pat. No. 3,254,111, each of which is hereby incorporated by reference herein. For example, the alpha-cyanoacrylates can be prepared by reacting an alkyl cyanoacetate with formaldehyde in a non-aqueous organic solvent and in the presence of a basic catalyst, followed by pyrolysis of the anhydrous intermediate polymer in the presence of a polymerization inhibitor. The alpha-cyanoacrylate monomers prepared with low moisture content and essentially free of impurities are preferred for biomedical use.

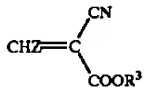
The alpha-cyanoacrylates of formula (II) wherein R^3 is a group having the formula $-R^4-O-R^5-O-R^6$ can be prepared according to the method disclosed in U.S. Pat. No. 4,364,876 (Kimura et al.), which is hereby incorporated by reference herein. In the Kimura et al. method, the alpha-cyanoacrylates are prepared by producing a cyanoacetate by esterifying cyanoacetic acid with an alcohol or by transesterifying an alkyl cyanoacetate and an alcohol; condensing the cyanoacetate and formaldehyde or paraformaldehyde in the presence of a catalyst at a molar ratio of 0.5–1.5:1, preferably 0.8–1.2:1, to obtain a condensate; depolymerizing the condensation reaction mixture either directly or after removal of the condensation catalyst to yield crude cyanoacrylate; and distilling the crude cyanoacrylate to form a high purity cyanoacrylate.

The alpha-cyanoacrylates of formula (II) wherein R^3 is a group having the formula



can be prepared according to the procedure described in U.S. Pat. No. 3,995,641 (Kronenthal et al.), which is hereby incorporated by reference. In the Kronenthal et al. method, such alpha-cyanoacrylate monomers are prepared by reacting an alkyl ester of an alpha-cyanoacrylic acid with a cyclic 1,3-diene to form a Diels-Alder adduct which is then subjected to alkaline hydrolysis followed by acidification to form the corresponding alpha-cyanoacrylic acid adduct. The alpha-cyanoacrylic acid adduct is preferably esterified by an alkyl bromoacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct. Alternatively, the alpha-cyanoacrylic acid adduct may be converted to the alpha-cyanoacrylyl halide adduct by reaction with thionyl chloride. The alpha-cyanoacrylyl halide adduct is then reacted with an alkyl hydroxyacetate or a methyl substituted alkyl hydroxyacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct or carbalkoxy alkyl alpha-cyanoatryate adduct, respectively. The cyclic 1,3-diene blocking group is finally removed and the carbalkoxy methyl alpha-cyanoacrylate adduct or the carbalkoxy alkyl alpha-cyanoacrylate adduct is converted into the corresponding carbalkoxy alkyl alpha-cyanoacrylate by heating the adduct in the presence of a slight deficit of maleic anhydride.

Examples of monomers of formula (II) include cyanopentadienoates and alpha-cyanoacrylates of the formula:



(III)

wherein Z is —CH=CH$_2$ and R^3 is as defined above. The monomers of formula (III) wherein R^3 is an alkyl group of 1–10 carbon atoms, i.e., the 2-cyanopenta-2,4-dienoic acid esters, can be prepared by reacting an appropriate 2-cyanoacetate with acrolein in the presence of a catalyst such as zinc chloride. This method of preparing 2-cyanopenta-2,4-dienoic acid esters is disclosed, for example, in U.S. Pat. No. 3,554,990, which is incorporated by reference herein.

Compositions of this invention comprise an effective amount of a biocompatible pH modifier to regulate the pH of an immediate in situ environment of the polymer to a pH level at which the polymer's in vivo biodegradation proceeds at a different rate than it does at a physiologic pH ("effective amount"). An effective amount of a pH modifier effective to achieve the desired in situ pH modification will depend on the acidity or basicity (pKa or pKb) of the compound used, the pH of the polymer composition used when in situ, the in vivo environment's physiologic pH, and the release rate of biodegradation products resulting from the pH-modified biodegradation rate. An effective amount of pH modifier may be selected with regard to any formaldehyde scavenger or other component added to control levels of biodegradation products released. As well, a non-toxic pH modifier (e.g., an acid) is preferably used, or the pH modifier is used in an effective amount that minimizes any potential toxic effect.

For instance, in embodiments of the invention, a non-encapsulated, acidic pH modifier may be present in an effective amount greater than 1% by weight of the composition. In microencapsulated forms, the amount of pH modifier added may be varied from a minimum effective amount up to a maximum loading permitted by the microcapsule and any toxicity limit, according to the particular monomer or polymer composition and application. At the same time, the pH modifier should not significantly affect inhibit (or accelerate) in vivo polymerization of the monomer composition or otherwise interfere with the composition's efficacy for medical or surgical applications.

An acidic or basic pH modifying compound, and its concentration in the composition, may be selected according to the in vivo pH range to be achieved in an immediate environment of the in situ polymerized or cross-linked adhesive composition. The desired in situ pH level depends on the particular monomer or polymer used and on whether that polymer's in vivo biodegradation rate is desired to be slower or faster than its biodegradation rate at the physiologic pH of the particular in vivo application. One skilled in the biocompatible monomer and polymer field will be able, upon reading this disclosure and with some routine experimentation, to select the pH modifier best suited for a given polymer or monomer composition and the particular application for which it is used.

The pH modifier may be selected to modify, in vivo, the pH of an immediate in situ environment of the polymer to a pH level at which in vivo biodegradation of the in situ polymer (and low molecular weight materials in the composition) proceeds more slowly than it does at a physiologic pH. This results in retarding the rate of release of formaldehyde and other degradation products, thereby reducing their toxic effects since, e.g., formaldehyde can be more completely eliminated before substantial, toxic concentrations occur in situ.

In such embodiments, the pH modifier may include, for example, but is not limited to, an acidic compound or anhydrous precursor thereof or a chemically protected acid. For example, the pH modifier may comprise at least one member selected from the group consisting of: amino acids; carboxylic acids and salts thereof; di-acids and salts thereof; poly-acids and salts thereof; esters that are easily hydrolyzable in vivo; lactones that are easily hydrolyzable in vivo; organic carbonates; enolic compounds; acidic phenols; polyphenolic compounds; aromatic alcohols; ammonium compounds or salts thereof; boron-containing compounds; sulfonic acids and salts thereof; sulfinic acids and salts thereof; phosphorus-containing compounds; acid halides; chloroformates; acid gases; acid anhydrides; inorganic acids and salts thereof; and polymers having functional groups of at least one of the preceding members. The pH modifier of this invention may, for example, comprise at least one member selected from the group consisting of: glycine; alanine; proline; lysine; glutaric acid; D-galacturonic acid; succinic acid; lactic acid; glycolic acid; poly(acrylic acid); sodium acetate; diglycolic anhydride; succinic anhydride; citraconic anhydride; maleic anhydride; lactide; diethyl oxalate; Meldrum's acid; diethyl carbonate; dipropyl carbonate; diethyl pyrocarbonate; diallyl pyrocarbonate; di-tert-butyl dicarbonate; ascorbic acid; catechin; ammonium chloride; D-glucosamine hydrochloride; 4-hydroxyephedrine hydrochloride; boric acid; nitric acid; hydrochloric acid; sulfuric acid; ethanesulfonic acid; and p-toluenesulfonic acid; 2-aminoethylphosphoric acid; methylphosphonic acid; dimethylphosphinic acid; methyl chloroformate; sulfur dioxide; and carbon dioxide. Glutaric acid and diethyl carbonate are particularly preferred in embodiments of the invention.

The pH modifier may alternatively be selected to modify, in vivo, a pH of an immediate in vivo environment of the polymer to a pH level at which in vivo biodegradation of the in situ polymer proceeds more quickly than it does at a physiologic pH. Basic pH modifiers allow the use of polymer materials otherwise degrading slowly or not at all in vivo, e.g., butyl alpha-cyanoacrylate or 2-octyl alpha-cyanoacrylate. The pH modifier is added in an amount sufficient to accelerate the polymer's biodegradation, but the accelerated release of biodegradation products (e.g., formaldehyde) must remain within physiologically tolerable ranges. In this aspect, a formaldehyde scavenger may also be added to keep formaldehyde levels within tolerable levels, for instance, in the manner of related application, U.S. Ser. No. 08/040,618.

In such embodiments, the pH modifier may include a basic compound or anhydrous precursor thereof, and/or a chemically protected base. For example, the pH modifier may comprise at least one member selected from the group consisting of: hydroxides; alkoxides; basic carbonates; nitrogen-containing compounds; amines; alkaloids; hydrides; organolithium compounds; Grignard reagents; carbanions; and polymers having functional groups of at least one of the preceding members. The pH modifier (whether single or in combination) may be, for example, selected from the group consisting of: sodium hydroxide; potasium hydroxide; sodium methoxide; potasium t-butoxide; sodium carbonate; calcium carbonate; dibutylamine; tryptamine; sodium hydride; calcium hydride; butyllithium; and ethylmagnesium bromide.

The present invention encompases situations in which formaldehyde is released as a byproduct of in situ biodegradation of the biocompatible polymer. A formaldehyde concentration-reducing agent or formaldehyde scavenger, e.g., sodium bisulfite, may be added to the compositions and methods of this invention to control formaldehyde release in situ and to minimize harmful effects therefrom, as disclosed in related application, U.S. Ser. No. 08/040,618, incorporated herein by reference. However, an acid pH modifier-containing composition herein disclosed can further minimize active formaldehyde concentrations in situ in the following manner. The pH modifier regulates the immediate pH environment of the in situ polymerized composition such that the polymer's in situ biodegradation is slowed, thereby keeping in situ formaldehyde concentrations at a level that can be handled physiologically and that will not, in an initial burst, overwhelm any formaldehyde scavenger that is present.

The pH modifier used in this invention may either be in free form or in a protected form. For instance, it may be in a form that is insoluble in the monomer of a monomer composition, such as a free acid or a microencapsulated form, or may be in a chemically protected form that may be soluble or insoluble in such monomer compositions. Once in vivo, the pH modifier may diffuse through the microcapsule or be released by bioerosion of the microcapsule, into the in situ polymer. The microcapsule may be formulated so that the pH modifier is released from the microcapsule continuously over a period of time during the biodegradation of the in situ polymer. Alternatively, the microencapsulated pH modifier may be formed to release rapidly and transiently, after a time delay, or even intermittently, vis-à-vis the life of the in situ polymer, depending on when the pH modifier is desired to have effect. For example, delayed release of a basic pH modifier may be desired to cause the polymer to begin to degrade rapidly after it has served a significant portion of its useful life. As well, pH modifiers may be used in combination, allowing, e.g., quick release of an acidic pH modifier followed by later release of a basic pH modifier, for more refined control of the polymer's biodegradation.

For purposes of this invention, the microencapsulated form of the pH modifier is advantageous because this embodiment prevents or substantially reduces preapplication effects of the pH modifier, e.g., a basic pH modifier, thereby increasing shelf-life and facilitating handling of the monomer composition during use.

Microencapsulation of the pH modifier can be achieved by many known microencapsulation techniques. For example, microencapsulation can be carried out by disolving a coating polymer in a volatile solvent, e.g., methylene chloride, to a polymer concentration of about 6% by weight; adding a pH modifying compound (selected to be acidic or basic according to the pH level to be achieved in situ) in particulate form to the coating polymer/solvent solution under agitation, to yield a pH modifier concentration of 2% to 10% by weight; adding the resulting polymer dispersion to a methylene chloride solution containing a phase inducer, such as silicone oil, under agitation; allowing the mixture to equilibrate for about 20 minutes; further adding the mixture slowly to a non-solvent, such as heptane, under rapid agitation; allowing the more volatile solvent to evaporate under agitation; removing the agitator; separating the solids from the silicone oil and heptane; and washing and drying the microparticles. The size of the microparticles will range from about 0.001 to about 1000 microns.

The microencapsulating coating polymer should be able to undergo in vivo bioerosion or to permit diffusion of the pH modifier, and should have low inherent moisture content. Bioerosion preferably occurs at rates greater than or similar to the rate of degradation of the base polymer. Such "bioerosion" can occur as a result of the physical or chemical breakdown of the encapsulating material, for example, by the encapsulating material passing from solid to solute in the presence of body fluids, or by biodegradation of the encapsulating material by agents present in the body.

Examples of coating materials that can be used to microencapsulate the pH modifier include, but are not limited to: polyesters, such as polyglycolic acid, polylactic acid, copolymers of polyglycolic acid and polylactic acid, polycaprolactone, poly-β-hydroxybutyrate, copolymers of ε-caprolactone and δ-valerolactone, copolymers of ε-caprolactone and DL-dilactide, and polyester hydrogels; polyvinylpyrrolidone; polyamides; gelatin; albumin; proteins; collagen; poly(orthoesters); poly(anhydrides); poly (alkyl-2-cyanoacrylates); poly(dihydropyrans); poly (acetals); poly(phosphazenes); poly(urethanes); poly (dioxinones); cellulose; and starches.

Examples of a phase inducer that can be added include silicone oil, mineral oil, polyethylene, polyisobutylene, and polybutadiene.

Compositions of this invention may further contain a stabilizer and/or one or more adjuvant substances, such as thickening agents, plasticizers, or the like, to improve its medical utility for particular medical applications.

Examples of suitable stabilizers include sulfur dioxide, sulfonic acid, lactone, boron trifluoride, hydroquinone, hydroquinone monomethyl ether, catechol, pyrogallol, benzoquinone, 2-hydroxybenzoquinone, p-methoxy phenol, t-butyl catechol, organic acid, butylated hydroxy anisole, butylated hydroxy toluene, t-butyl hydroquinone, alkyl sulfate, alkyl sulfite, 3-sulfolene, alkylsulfone, alkyl sulfoxide, mercaptan, and alkyl sulfide.

Suitable thickeners include, for example, polycyanoacrylates, polylactic acid, polyglycolic acid,

lactic-glycolic acid copolymers, polycaprolactone, lactic acid-caprolactone copolymers, poly-3-hydroxybutyric acid, polyorthoesters, polyalkyl acrylates, copolymers of alkylacrylate and vinyl acetate, polyalkyl methacrylates, and copolymers of alkyl methacrylates and butadiene.

Examples of suitable plasticizers include dioctyl phthalate, dimethyl sebacate, triethyl phosphate, tri(2-ethylhexyl)phosphate, tri(p-cresyl) phosphate, glyceryl triacetate, glyceryl tributyrate, diethyl sebacate, dioctyl adipate, isopropyl myristate, butyl stearate, lauric acid, dibutyl phthalate, trioctyl trimellitate, and dioctyl glutarate.

To improve the cohesive strength of adhesives formed from the compositions of this invention, difunctional monomeric cross-linking agents may be added to compositions or used in methods of this invention in vivo or ex vivo. Such crosslinking agents are known. Reference is made, for example, to U.S. Pat. No. 3,940,362 (Overhults), which is hereby incorporated by reference herein. Examples of suitable crosslinking agents include alkyl bis(2-cyanoacrylates), triallyl isocyanurates, alkylene diacrylates, alkylene dimethacrylates, trimethylol propane triacrylate, and alkyl bis(2-cyanoacrylates). When used ex vivo, a catalytic amount of a free radical initiator is added to initiate polymerization of the cyanoacrylate monomer/crosslinking agent blend. Such compositions can be molded or otherwise formed to provide preformed implants and prosthetic devices for surgical use, such as rods, meshes, plates, screws, and fasteners.

The compositions of this invention may further contain fibrous reinforcement and colorants, e.g., dyes and pigments. Examples of suitable fibrous reinforcement include PGA microfibrils, collagen microfibrils, cellulosic microfibrils, and olefinic microfibrils. Examples of suitable colorants include 1-hydroxy-4-[4-methylphenylamino]-9,10 anthracenedione (FD&C violet No. 2); disodium salt of 6-hydroxy-5-[(4-sulfophenyl)axo]-2-naphthalenesulfonic acid (FD&C Yellow No. 6); 9-(o-carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthen-3-one, disodium salt, monohydrate (FD&C Red No. 3); 2-(1,3-dihydro-3-oxo-5-sulfo-2H-indol-2-ylidene)-2,3-dihydro-3-oxo-1H-indole-5-sulfonic acid disodium salt (FD&C Blue No. 2); and [phthalocyaninato (2-)] copper.

The biocompatible adhesive compositions of this invention can be used, for example, to Join together two surfaces, at least one of the surfaces being body or living tissue, by applying the composition to at least one of the surfaces. Depending on the particular requirements of the user, the compositions of this invention can be applied by known means, such as with a glass stirring rod, sterile brush, medicine dropper, spray bottle or other non-aerosol means. However, in many situations, a presurized aerosol dispensing package is advantageous, in which the adhesive composition is in solution with a compatible anhydrous or other aerosol propellant. Aerosol application of the monomers is particularly advantageous for use in hemostasis. The compositions of this invention may also be stored in and dispensed from a two-phase container, in which the pH modifier is kept apart from the monomer composition until shortly before or at the moment of applying the adhesive composition in situ to the in vivo surfaces to be bonded. If a formaldehyde concentration-reducing agent is also present, it may be present in either of the above two phases, or in a separate third phase of a multi-phase container.

In one embodiment, the present invention is directed to a method of joining together in vivo two surfaces, one or both of which may be a body tissue, which comprises (a) applying to at least one of said surfaces a biocompatible composition of this invention, and (b) maintaining the surfaces in contact until said composition joins together the two surfaces (e.g., by polymerization of the monomer composition). One of said surfaces can be body tissue and the other surface a prosthetic device or the like, or both surfaces may be body tissue. As one example of a composition which may be used to practice this method, said composition may comprise: (1) at least one monomer (e.g., a monomer of formula (I)) which forms a polymer whose in vivo biodegradation proceeds at a physiologic pH (and may release formaldehyde); and (2) an effective amount of a biocompatible pH modifier to regulate the pH of an immediate in situ environment of the biocompatible polymer to a pH level at which said polymer biodegrades at a different rate than it does at said physiologic pH. The pH modifier may be selected to slow or to accelerate the polymer's biodegradation.

Various methods for repairing or strengthening damaged living tissue to prevent the escape of fluids therethrough exist which may employ a composition of the invention. For example, a method for repairing or dresing living tissue may comprise: (a) applying to the tissue a surgical sealant comprising the biocompatible composition including a pH modifier of this invention; and (b) allowing the composition to polymerize. A method for stemming the flow of blood from small vessels may comprise applying to said vessels a surgical sealant or hemostatic agent comprising a biocompatible monomer composition including a pH modifier. A method of dresing burns to promote the healing thereof may comprise (a) covering said burn with a biocompatible composition of this invention; and (b) allowing the composition to polymerize in situ; and methods of dresing wounds to promote the healing thereof may comprise (a) covering said wound with a biocompatible composition of this invention; and (b) allowing the composition to polymerize.

Repairing injured tissues (for example, to control bleeding) may comprise, for example, sponging to remove superficial body fluids and subsequent application to the exposed tissue of a composition of the invention. For example, a monomer composition polymerizes to a thin film of polymer while in contact with the tissue surface. For bonding separate surfaces of body tissues, the monomer is applied to at least one surface, and the surfaces are brought quickly together while the monomer polymerizes in contact with both surfaces.

In another embodiment, the present invention may be used in a method for effecting in vivo administration of a bioactive agent, comprising introducing into a body a composition of this invention, which may comprise: (a) a polymer whose in vivo biodegradation may or may not release formaldehyde; (b) an effective amount of a biocompatible pH modifier; and (c) a bioactive amount of a bioactive agent, wherein biodegradation of the polymer or diffusion of the bioactive agent effects its in vivo release. The bioactive agent may be encapsulated in a suitable biodegradable material for controlling release of the bioactive agent. The polymer may be one degrading slowly or not at all or may be hydrolytically sensitive, at an in vivo physiologic pH. In the former case, a basic pH modifier may be added to promote biodegradation of the polymer. The composition may also include an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels, e.g., a formaldehyde scavenger.

The compositions may be used further to administer therapeutic agents into the body. The composition will form a matrix for the therapeutic agent, with the therapeutic agent being released in vivo from the matrix by diffusion or by biodegradation, over time, of the polymer. For example, a

composition comprising the monomer (or polymer form of the monomer, since in this application, polymerization need not occur in situ), a biocompatible pH modifier of this invention, an optional biocompatible formaldehyde scavenger, and a therapeutic agent are introduced into the body where the polymer undergoes biodegradation, gradually releasing the therapeutic agent. Alternatively, the therapeutic agent may diffuse out from the composition, into the body, before polymeric biodegradation ends or even begins.

The monomers are readily polymerized to additiontype polymers and copolymers.

In most bonding applications using compositions of this invention, polymerization of the monomers is catalyzed by small amounts of moisture on the surface of the adherents. Therefore, desired bonding of tissues and hemostasis proceed well in the presence of blood and other body fluids. The bonds formed are of adequate flexibility and strength to withstand normal movement of tissue. In addition, bond strength is maintained as natural tissue healing proceeds concurrently with polymer asimilation.

Compositions employed in the invention are sterilizable by conventional methods such as by autoclave or by aseptic filtration techniques.

The invention is further illustrated by the following non-limiting examples.

EXAMPLES

In the Examples below, the following terms are defined as follows:

IPECA—2-isopropoxyethyl cyanoacrylate

DMM—dimethyl 2-methylenemalonate

3MBCA—3-methoxybutyl cyanoacrylate

20CA—2-octyl cyanoacrylate

monomer(s)—refers generically to IPECA, DMM, 3MBCA and/or 20CA

Examples 1–18 and Control Examples 1C–18C

Examples 1–18 and Control Examples 1C–18C illustrate the effect of a biocompatible pH modifier on the biodegradation of a 1,1-disubstituted ethylene monomer polymerized in situ. The compositions of Examples 1–18 each contain a pH modifier (in free or microencapsulated form) while the compositions of Control Examples 1C–18C contain sodium chloride (NaCl), polycaprolactone microcapsules, or no additive.

The formulations of the compositions prepared in Examples 1–18 and Control Examples 1C–18C are shown in Tables IA and IB, respectively.

The compositions of the examples are prepared as follows. Appropriate weight ratios of the monomer and an additive are mixed thoroughly by shaking. (Solid pH modifiers and sodium chloride are ground or milled to a fine particle size before mixing.) The resulting mixture is quickly poured onto a glass plate equipped with a 4 cm ×8 cm boundary. The glass plate is pre-treated with chlorotrimethylsilane and the boundary is fabricated with caulking cord material. The mixture is spread evenly to all edges. Polymerization of the monomer mixture is then accelerated by spraying with a 1% aqueous sodium bicarbonate solution (Examples 1–3, 5, 9–18, 1C–3C, 5C, and 9C–18C) or a 1:2:97 triethylamine/methanol/heptane mixture (Examples 4, 6–8, 4C, and 6C–8C). The hardened polymer film is gently scraped off the glass plate, cut away from the boundary and dried. It is further cut into two halves, each of 2 cm×8 cm, for duplicate runs.

In Examples 13–15, the additive is sprinkled evenly on the glass plate and the monomer is then carefully added, instead of the two being mixed directly.

In vitro biodegradation (simulating in vivo biodegradation) of each 2 cm×8 cm polymer film is then carried out as follows. The polymer film, encaged in aluminum mesh, is placed in a pH 7.4 buffer (e.g., monobasic potasium phosphate and dipotasium phosphate). Biodegradation is carried out at 37±2° C. for 168 hours (Examples 1–9, 13–18, 1C–9C, and 13C–18C) or at 37±2° C. for 192 hours (Examples 10–12, and 10C–12C). The partially degraded film is separated from the buffer solution and dried. The buffer solution is subjected to formaldehyde determination.

Determination of the amount of formaldehyde generated during biodegradation of the polymer films may be accomplished as disclosed in related application U.S. Ser. No. 08/040,618 (U.S. Pat. No. 5,328,687).

In the following tables, the term "μg formaldehyde detected per g polymer" means the amount of formaldehyde generated in micrograms divided by the original polymer weight in grams (excluding the weight of the pH modifier or control additive).

TABLE IA

Examples 1–18

Example No.	Monomer	Additive	Additive Weight %	μg Formaldehyde Detected per g Polymer	% Change of Formaldehyde Detected
1	IPECA	diethyl carbonate	2.5	1652	−77.4
2	IPECA	diethyl carbonate	5.0	1278	−87.0
3	IPECA	diethyl carbonate	7.5	8806	−14.4
4	IPECA	lactide	7.0	1161	−73.3
5	IPECA	glucosamine hydrochloride	9.0	6082	−19.9
6	IPECA	ascorbic acid	2.0	5226	−66.7
7	IPECA	glutaric acid	1.0	13,788	−7.3
8	IPECA	glutaric acid polycaprolactone microcapsules	8.0	3023	−20.0
9	3MBCA	glycine	8.0	1909	−8.7
10	DMM	diethyl oxalate	6.0	1723	−61.4
11	DMM	tryptamine	3.0	2538	+22.6

TABLE IA-continued

Examples 1–18

Example No.	Monomer	Additive	Additive Weight %	μg Formaldehyde Detected per g Polymer	% Change of Formaldehyde Detected
12	DMM	potassium carbonate	2.0	2372	+16.2
13	IPECA	tryptamine/polycaprolactone microcapsules	4.0	10,376	+53.4
14	IPECA	tryptamine/polycaprolactone microcapsules	6.0	9961	+63.7
15	IPECA	tryptamine/polycaprolactone microcapsules	8.0	9094	+46.9
16	IPECA	sodium carbonate/polycaprotactone microcapsules	10.0	6949	+63.6
17	3MBCA	sodium methoxide	5.0	4389	+856.2
18	20CA	sodium hydroxide	8.5	2351	+1379.0

TABLE IB

Control Examples 1C–18C

Example No.	Monomer	Additive	Additive Weight %	μg Formaldehyde Detected per g Polymer	% Change of Formaldehyde Detected
1C	IPECA	sodium chloride	2.5	7295	0
2C	IPECA	sodium chloride	5.0	9856	0
3C	IPECA	sodium chloride	7.5	10,293	0
4C	IPECA	sodium chloride	7.0	4355	0
5C	IPECA	sodium chloride	9.0	7595	0
6C	IPECA	sodium chloride	2.0	15,698	0
7C	IPECA	sodium chloride	1.0	14,880	0
8C	IPECA	sodium chloride	8.0	3780	0
9C	3MBCA	sodium chloride	8.0	2091	0
10C	DMM	sodium chloride	6.0	4466	0
11C	DMM	sodium chloride	3.0	2070	0
12C	DMM	sodium chloride	2.0	2041	0
13C	IPECA	polycapralactone microcapsules	4.0	6764	0
14C	IPECA	polycaprolactone microcapsules	6.0	6085	0
15C	IPECA	polycaprolactone microcapsules	8.0	6189	0
16C	IPECA	polycaprolactone microcapsules	10.0	4248	0
17C	3MBCA	none	0	459	0
18C	20CA	none	0	159	0

The monomer IPECA is polymerized by azoisobutyronitrile (AIBN) at 70° C. to give a polymer of approximately 25,000 molecular weight. In the following Examples, polymer(s) refers generically to the IPECA polymer prepared in this manner.

Examples 19–20 and Control Examples 19C–20C

Examples 19–20 and Control Examples 19C–20C illustrate the effect of a biocompatible pH modifier on the biodegradation of a 1,1-disubstituted ethylene polymer. The compositions of Examples 19–20 each contain a pH modifier while the compositions of Control Examples 19C–20C contain sodium chloride (NaCl).

The formulations of the compositions prepared in Examples 19–20 and Control Examples 19C–20C are shown in Table II.

The compositions of the examples are prepared as follows. The polymer is disolved in methylene chloride to give a polymer concentration of about 15%. The resulting polymer solution and an additive (either a pH modifier or sodium chloride) are mixed thoroughly in the appropriate weight ratio by shaking. (Solid pH modifiers and sodium chloride are ground or milled to a fine particle size before mixing.) The resulting mixture is quickly poured onto a glass plate equipped with a 4 cm×8 cm boundary. The glass plate is pre-treated with chlorotrimethylsilane and the boundary is fabricated with caulking cord material. The inside border is painted with melted paraffin wax. The mixture is spread evenly to all edges. Following evaporation of solvent, the polymer film is gently scraped off the glass plate, cut away from the boundary and dried. It is further cut into two halves, each of 2 cm×8 cm, for duplicate runs.

In vitro biodegradation (simulating in vivo biodegradation) of the polymer films and formaldehyde determination are carried out using the same procedures followed in Examples 1–9 and 13–18 and Control Examples 1C–9C and 13C–18C. The results of Examples 19–20 and

Control Examples 19C–20C are shown in Table II.

TABLE II

Examples 19–20 and Control Examples 19C–20C

Example No.	Polymer Additive	Additive Weight %	μg Formaldehyde Detected per g Polymer	% Change of Formaldehyde Detected
19	IPECA hydrochloric acid	1.0	329	−37.0
20	IPECA methylphosphonic acid	5.0	906	−55.1
19C	IPECA sodium chloride	1.0	522	0
20C	IPECA sodium chloride	5.0	2018	0

We claim:

1. A method comprising:

(a) applying to an in vivo surface a biocompatible composition comprising:

(1) at least one monomer which forms a polymer in situ at a physiologic pH; and

(2) an effective amount of at least one biocompatible pH modifier to modify the pH of an immediate in vivo environment of said polymer to a pH range at which said polymer biodegrades at a different rate than it does at physiologic pH, without said pH modifier significantly affecting the monomer's polymerization in situ, said at least one biocompatible pH modifier being thoroughly mixed with said at least one monomer; and

(b) allowing the monomer composition to polymerize in situ,

wherein said pH modifier is in at least one form selected from the group consisting of:

(a) insoluble in the monomer,

(b) in a microcapsule,

(c) chemically protected and insoluble in the monomer,

(d) chemically protected and basic,

(e) acidic and chemically protected form of at least one member selected from the group consisting of amino acids; di-acids and salts thereof; polyacids and salts thereof; esters that are easily hydrolyzable in vivo; lactones that are easily hydrolyzable in vivo; organic carbonates; enolic compounds; acidic phenols; polyphenolic compounds; aromatic alcohols; boron-containing compounds; sulfonic acids and salts thereof; sulfinic acids and salts thereof; phosphorus-containing compounds; acid halides; chloroformates; acid gases; acid anhydrides; inorganic acids and salts thereof; and polymers having functional groups of at least one member selected from the group consisting of amino acids, di-acids and salts thereof, polyacids and salts thereof, lactones that are easily hydrolyzable in vivo, organic carbonates, enolic compounds, acidic phenols, polyphenolic compounds, aromatic alcohols, boron-containing compounds, sulfonic acids and salts thereof, sulfinic acids and salts thereof, phosphorus-containing compounds, acid halides, chloroformates, acid gases, acid anhydrides, and inorganic acids and salts thereof, and

(f) acidic and chemically protected form of at least one member selected from the group consisting of D-galacturonic acid; succinic acid and succinic anhydride; glycolic acid; poly(acrylic acid); acetic acid; diglycolic ahyhdride; citraconic anhydride; maleic anhydride; diethyl oxalate; Meldrum's acid; diethyl carbonate; dipropyl carbonate; diethyl pyrocarbonate; diallyl pyrocarbonate; di-tert-butyl dicarbonate; ascorbic acid; catechin; D-glucosamine hydrochloride; 4-hydroxy-ephedrin hydrochloride; boric acid; nitric acid; hydrochloric acid; sulfuric acid; ethanesulfonic acid; p-toluenesulfonic acid; 2-aminoethylphosphoric acid; methylphosphonic acid; dimethylphosphinic acid; methyl chloroformate; sulfur dioxide; carbon dioxide; and combinations of the above materials.

2. The method of claim 1, wherein said composition is an adhesive composition, and said surface is maintained in contact with another surface in vivo until the monomer composition polymerizes.

3. The method of claim 2, wherein one of the surfaces is body tissue and the other surface is a prosthetic device.

4. The method of claim 2, wherein both surfaces are body tissue.

5. The method of claim 1, wherein said composition is applied to damaged or exposed tissue.

6. The method of claim 5, wherein said tissue comprises a blood vessel, and said method stems flow of blood from said blood vessel by applying to said blood vessel a hemostatic agent comprising said composition.

7. The method of claim 5, wherein said tissue has been burned or is living tissue exposed in a wound.

8. The method of claim 1, wherein the pH modifier is soluble in the monomer.

9. The method of claim 1, wherein the polymer's in vivo biodegradation proceeds faster than it does at physiologic pH.

10. The method of claim 1, wherein the polymer's in vivo biodegradation proceeds slower than it does at physiologic pH.

11. The method of claim 1, wherein the polymer degrades slowly or not at all at a physiologic pH and the pH modifier is a basic compound.

12. The method of claim 1, wherein the polymer comprises at least one member selected from the group consisting of butyl alpha-cyanoacrylate and octyl alpha-cyanoacrylate, and said pH modifier is a basic compound.

13. The method of claim 1, wherein the composition further comprises at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

14. The method of claim 9, wherein the composition further comprises at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

15. The method of claim 1, wherein the monomer is an alpha-cyanoacrylate or a 2-methylene malonate.

16. The method of claim 15, wherein the alpha-cyanoacrylate is methyl cyanoacrylate, butyl cyanoacrylate, 2-octyl cyanoacrylate, 1-methoxy-2-propyl cyanoacrylate, 2-butoxyethyl cyanoacrylate, 2-isopropoxyethyl cyanoacrylate or 3-methoxybutyl cyanoacrylate.

17. The method of claim 1, wherein the pH modifier is microencapsulated in a material that has a low inherent moisture content and that undergoes in vivo bioerosion.

18. The method of claim 1, wherein the pH modifier is microencapsulated in a material and is capable, in vivo, of diffusing through the material.

19. The method of claim 1, wherein the pH modifier is in chemically protected acidic form.

20. The method of claim 1, wherein the pH modifier comprises at least one member selected from the group consisting of: glycine; alanine; proline; lysine; glutaric acid; D-galacturonic acid; succinic acid; tactic acid; glycolic acid; poly(acrylic acid); sodium acetate; diglycolic anhydride; succinic anhydride; citraconic anhydride; maleic anhydride; lactide; diethyl oxalate; Meldrum's acid; diethyl carbonate; dipropyl carbonate; diethyl pyrocarbonate; diallyl pyrocarbonate; di-tert-butyl dicarbonate; ascorbic acid; catechin; ammonium chloride; D-glucosamine hydrochloride; 4-hydroxyephedrine hydrochloride; boric acid; nitric acid; hydrochloric acid; sulfuric acid; ethanesulfonic acid; p-toluenesulfonic acid; 2-aminoethylphosphoric acid; methylphosphonic acid; dimethylphosphinic acid; and methyl chloroformate.

21. The method of claim 1, wherein the pH modifier comprises at least one member selected from the group consisting of:

hydroxides;

alkoxides;

basic carbonates;

alkaloids;

hydrides;

organolithium compounds;

Grignard reagents;

carbanions;

chemically protected bases; and

polymers having functional groups of at least one of the preceding members.

22. The method of claim 1, wherein the pH modifier comprises at least one member selected from the group consisting of: sodium hydroxide; potasium hydroxide; sodium methoxide; potasium t-butoxide; sodium carbonate; dibutylamine; tryptamine; sodium hydride; calcium hydride; butyllithium; and ethylmagnesium bromide.

23. A method of regulating a rate of in vivo biodegradation of a polymer formed in vivo from at least one monomer that forms a polymer at a physiologic pH, comprising:

combining said at least one monomer with an effective amount of at least one biocompatible pH modifier to modify a pH of an immediate in situ environment of the polymer to a pH range at which the polymer's biodegradation proceeds at a different rate than it does at physiologic pH;

allowing the polymer to form in vivo; and

maintaining the thus-formed polymer in vivo for a time sufficient to effect biodegradation of the polymer,

wherein said pH modifier is in at least one form selected from the group consisting of:

(a) insoluble in the monomer,

(b) in a microcapsule,

(c) chemically protected and insoluble in the monomer,

(d) chemically protected and basic,

(e) acidic and chemically protected form of at least one member selected from the group consisting of amino acids; di-acids and salts thereof; polyacids and salts thereof; esters that are easily hydrolyzable in vivo; lactones that are easily hydrolyzable in vivo; organic carbonates; enolic compounds; acidic phenols; polyphenolic compounds; aromatic alcohols; boron-containing compounds; sulfonic acids and salts thereof; sulfinic acids and salts thereof; phosphorus-containing compounds; acid halides; chloroformates; acid gases; acid anhydrides; inorganic acids and salts thereof; and polymers having functional groups of at least one member selected from the group consisting of amino acids, di-acids and salts thereof, polyacids and salts thereof, lactones that are easily hydrolyzable in vivo, organic carbonates, enolic compounds, acidic phenols, polyphenolic compounds, aromatic alcohols, boron-containing compounds, sulfonic acids and salts thereof, sulfinic acids and salts thereof, phosphorus-containing compounds, acid halides, chloroformates, acid gases, acid anhydrides, and inorganic acids and salts thereof, and

(f) acidic and chemically protected form of at least one member selected from the group consisting of D-galacturonic acid; succinic acid and succinic anhydride; glycolic acid; poly(acrylic acid); acetic acid; diglycolic ahyhdride; citraconic anhydride; maleic anhydride; diethyl oxalate; Meldrum's acid; diethyl carbonate; dipropyl carbonate; diethyl pyrocarbonate; diallyl pyrocarbonate; di-tert-butyl dicarbonate; ascorbic acid; catechin; D-glucosamine hydrochloride; 4-hydroxy-ephedrin hydrochloride; boric acid; nitric acid; hydrochloric acid; sulfuric acid; ethanesulfonic acid; p-toluenesulfonic acid; 2-aminoethylphosphoric acid; methylphosphonic acid; dimethylphosphinic acid; methyl chloroformate; sulfur dioxide; carbon dioxide; and combinations of the above materials.

24. The method of claim 23, wherein the polymer is a polymer of at least one 1,1-disubstituted ethylene monomer.

25. The method of claim 23, wherein the polymer is hydrolytically sensitive in vivo at a physiologic pH.

26. The method of claim 23, wherein the polymer biodegrades slowly or not at all at a physiologic pH, and the pH modifier is a basic compound.

27. The method of claim 23, wherein the polymer comprises at least one member selected from the group consisting of butyl alpha-cyanoacrylate and octyl alpha-cyanoacrylate, and said pH modifier is a basic compound.

28. The method of claim 1, wherein the monomer is a 1,1-disubstituted ethylene monomer.

29. The method of claim 1, wherein the monomer is an alkoxyalkyl cyanoacrylate monomer.

30. The method of claim 23, wherein the monomer is an alkoxyalkyl cyanoacrylate monomer.

* * * * *

Exhibit 5

US006174919B1

(12) United States Patent
Hickey

(10) Patent No.: US 6,174,919 B1
(45) Date of Patent: Jan. 16, 2001

(54) **CYANOACRYLATE COMPOSITIONS WITH VINYL TERMINATED ESTER GROUPS**

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(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/025,473**

(22) Filed: **Feb. 18, 1998**

(51) **Int. Cl.**[7] **A01N 37/34**

(52) **U.S. Cl.** **514/519**; 156/326; 156/330.9; 424/400; 424/443; 424/448; 424/487

(58) **Field of Search** 424/400, 443, 424/448, 487; 156/330.9, 326

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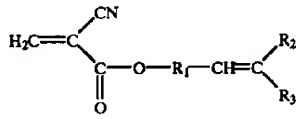
(57) **ABSTRACT**

An adhesive composition includes compounds having the following formula:



wherein R_1 is alkyl, alkoxy alkyl, anhydride, ether, ester, or amide, and R_2 and R_3 are hydrogen, alkyl, alkoxy alkyl, hydroxy, alkenyl, ester, carboxylic acid or ether and wherein R_1 is optionally omitted where R_2 and R_3 are not both hydrogen.

19 Claims, No Drawings

CYANOACRYLATE COMPOSITIONS WITH VINYL TERMINATED ESTER GROUPS

BACKGROUND OF THE INVENTION

1. Field of Invention

The present invention is directed to monomer compositions useful to form industrial, consumer or medical adhesives and sealants, and methods of applying such compositions. More particularly, this invention relates to monomeric cyanoacrylate compositions having vinyl terminated ester groups that allow a biologically acceptable method of crosslinking through the vinyl group.

2. Description of Related Art

U.S. Pat. No. 5,624,669 to Leung et al., discloses hemostatic procedures for sealing punctures and incisions in blood vessels and internal organs by applying a cyanoacrylate monomer. Although the cyanoacrylate may polymerize and/or cross-link in vivo, it preferably does so without the need for external sources of physical initiation such as irradiation.

U.S. Pat. No. 4,134,929 to Stoakley et al. discloses a polymerizable monomeric allyl 2-cyanoacrylate containing portion comprising an amount of an organic peroxide free radical providing compound sufficient to cause crosslinking of a difunctional monomer diester with the allyl 2-cyanoacrylate. Stoakley discloses that crosslinking may occur by way of the allyl group.

U.S. Pat. No. 4,136,138 to Dombroski et al. discloses a polymerizable monomeric 2-cyanoacrylate containing portion comprising an amount of an organic peroxide free radical providing compound sufficient to cause crosslinking of a difunctional monomer diester with the 2-cyanoacrylate. Dombroski discloses that the allyl 2-cyanoacrylate-based adhesive compositions are especially useful as dental adhesives.

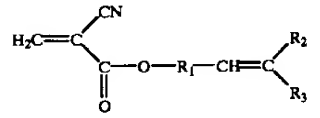
U.S. Pat. No. 3,975,422 to Buck discloses difunctional monomers where R is an organic linking group derived from a diol or a dihalide of the formula X—R—X, where X is either Cl, Br, I, or hydroxy. The difunctional monomers are employed as crosslinking agents for monofunctional esters of 2-cyanoacrylates. The monofunctional cyanoacrylate monomers may be cyanoacrylates that are terminated by an alkyl, cyclohexyl or phenyl group. Copolymerized compositions of the monomer blends (difunctional and monofunctional) are useful as adhesives in dental applications. The polymerization of these compositions is initiated by an anionic catalyst or by thermal or other means.

SUMMARY OF THE INVENTION

The present invention is directed to monomeric cyanoacrylate compositions having vinyl terminated ester groups that cross-link through the vinyl group, and biomedical uses of such compositions. Cross-linking occurs by way of the vinyl terminated ester groups. In embodiments, chemical durability, flexibility and elasticity of the resulting polymers or copolymers may be increased and degradability can be reduced. In addition, in embodiments high temperatures or ultraviolet initiators may not be needed for cross-linking.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Cyanoacrylate adhesive compositions of the invention contain compounds represented by the following formula (I):



(I)

wherein R_1 is alkyl, alkoxy, anhydride, ether, ester, or amide, and R_2 and R_3 are independently alkyl, alkoxy, hydrogen, hydroxy, alkenyl, ester, carboxylic acid, ether, or electron withdrawing groups such as halogens, amides, cyanos, esters, acids and ethers. Preferably, R_1 is an alkyl having from about 1 to 8 carbon atoms. Preferably, R_2 and R_3 are hydrogen atoms. More preferably, R_2 and R_3 are alkyl groups having from about 1 to 3 carbon atoms. The R_1 group extends the distance of the R_2 and R_3 groups away from the carbonyl group, thereby making them more chemically accessible and improving chemical durability, flexibility and elasticity of a polymer comprising the monomer. In embodiments, R_1 may be omitted if R_2 and R_3 are not both hydrogen.

In embodiments, the adhesive compositions may additionally contain heat and/or light (e.g., visible or ultraviolet light) activated initiators and accelerators that initiate crosslinking of the cyanoacrylate compounds.

Particular initiators for particular systems may be readily selected by one of ordinary skill in the art without undue experimentation. Suitable polymerization initiators for the cyanoacrylate compositions include, but are not limited to, detergent compositions; surfactants: e.g., nonionic surfactants such as polysorbate 20 (e.g., Tween 20™), polysorbate 80 (e.g., Tween 80™) and poloxamers, cationic surfactants such as tetrabutylammonium bromide, anionic surfactants such as benzalkonium chloride or its pure components, stannous octoate (tin (II) 2-ethylhexanoate), and sodium tetradecyl sulfate, and amphoteric or zwitterionic surfactants such as dodecyldimethyl(3-sulfopropyl)ammonium hydroxide, inner salt; amines, imines and amides, such as imidazole, tryptamine, urea, arginine and povidine; phosphines, phosphites and phosphonium salts, such as triphenylphosphine and triethyl phosphite; alcohols such as ethylene glycol, methyl gallate, ascorbic acid, tannins and tannic acid; inorganic bases and salts, such as sodium bisulfite, magnesium hydroxide, calcium sulfate and sodium silicate; sulfur compounds such as thiourea and polysulfides; polymeric cyclic ethers such as monensin, nonactin, crown ethers, calixarenes and polymeric epoxides; cyclic and acyclic carbonates, such as diethyl carbonate; phase transfer catalysts such as Aliquat 336; and organometallics such as cobalt naphthenate and manganese acetylacetonate and radical initiators.

Suitable initiators for both of the polymerization of the cyanoacrylate and cross-linking of the vinyl group of the composition include, but are not limited to, radicals, such as di-t-butyl peroxide, azobisisobutyronitrile and benzoylperoxide and sodium bisulfite. The polymerizable and/or cross-linkable material may also contain an initiator which is inactive until activated by a catalyst or accelerator (included within the scope of the term "initiator" as used herein). Accelerators for radical initiators such as dimethylaminopyridine and other aminopyridine type molecules may act as an initiator for the cyanoacrylate as well as for the radical polymerization of the vinyl moiety.

In embodiments, when R_1 is omitted and R_2 and/or R_3 are a moiety other than hydrogen, and the composition is to be cationically polymerizable, materials such as strong acids,

alkyl iodides (iodomethane), iodine, acetyl perchlorate, and Lewis acids (boron trifluoride, tin tetrachloride, aluminum trichloride, and organometallic derivatives, e.g., $RAlCl_2$, R_2AlCl, wherein R is an alkyl group and R_2 is two R groups) may be used.

The monomer compositions of the present invention and polymers formed therefrom are useful as tissue adhesives, sealants for preventing bleeding or for covering open wounds, and in other biomedical applications. They find uses in, for example, apposing surgically incised or traumatically lacerated internal and/or external tissues; setting fractured bone structures; retarding blood flow from wounds; drug delivery; dressing burns; and aiding repair and regrowth of living tissue.

Conventional surgical adhesive compositions have included plasticizers with the adverse effect of reducing the film strength. It has been discovered that, contrary to prior belief, the film strength (e.g., toughness) under certain conditions is not adversely reduced upon the addition of greater amounts of plasticizing agent. Depending on the particular acidic stabilizing agent and the purity of the monomer utilized in the adhesive composition, the addition of greater amounts of plasticizing agent may increase the toughness of the resulting bond formed on the wound. Acidic stabilizing agents do not significantly affect the polymerization of the monomer in the present composition and provide increased film strength with increasing amounts of plasticizing agents.

Monomers that may be used in this invention are polymerizable, e.g. anionically polymerizable or free radical polymerizable, to form polymers. In embodiments, the cyanoacrylate composition may comprise a homopolymer of the monomer of formula (I) or a copolymer or terpolymer with other monomers. Such other monomers include, but are not limited to, acrylate monomers, methacrylate monomers, and 1,1-disubstituted ethylene monomers of the formula:

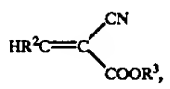
$$HRC{=}CXY \qquad (II)$$

wherein X and Y are each strong electron withdrawing groups, and R is H, $-CH{=}CH_2$, or an alkyl such as methyl, ethyl and other lower alkyls such as butyl and the like, provided that X and Y are both cyano groups, a C_1–C_4 alkyl group.

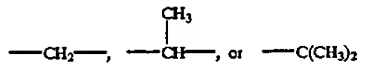
Examples of monomers within the scope of formula (II) include alpha-cyanoacrylates, vinylidene cyanides, C_1–C_4 alkyl homologues of vinylidene cyanides, dialkyl methylene malonates, acylacrylonitriles, vinyl sulfinates and vinyl sulfonates of the formula $H_2C{=}CX'Y'$ wherein X' is $-SO_2R'$ or $-SO_3R'$ and Y' is —CN, —COOR', $-COCH_3$, $-SO_2R'$ or $-SO_3R'$, and R' is H or hydrocarbyl.

Preferred monomers of formula (II) for use in this invention are alpha-cyanoacrylates. These monomers are known in the art and have the formula

(III)



wherein R^2 is hydrogen or lower alkyl and R^3 is a hydrocarbyl or substituted hydrocarbyl group including polymeric groups; a group having the formula $-R^4-O-R^5-O-R^6$, wherein R^4 is a 1,2-alkylene group having 2–4 carbon atoms, R^5 is an alkylene group having 2–4 carbon atoms, and R^6 is an alkyl group having 1–6 carbon atoms; or a group having the formula $-R^7-C(=O)-O-R^8$, wherein R^7 is



wherein n is 1–10, preferably 1–5 carbon atoms and R^8 is an organic moiety.

Examples of suitable hydrocarbyl and substituted hydrocarbyl groups include straight chain or branched chain alkyl groups having 1–16 carbon atoms; straight chain or branched chain C_1–C_{16} alkyl groups substituted with an acyloxy group, a haloalkyl group, an alkoxy group, a halogen atom, a cyano group, or a haloalkyl group; straight chain or branched chain alkenyl groups having 2 to 16 carbon atoms; straight chain or branched chain alkynyl groups having 2 to 12 carbon atoms; cycloalkyl groups; aralkyl groups; alkylaryl groups; and aryl groups.

The organic moiety R^8 may be substituted or unsubstituted and may be straight chain, branched or cyclic, saturated, unsaturated or aromatic. Examples of such organic moieties include C_1–C_8 alkyl moieties, C_2–C_8 alkenyl moieties, C_2–C_8 alkynyl moieties, C_3–C_{12} cycloaliphatic moieties, aryl moieties such as phenyl and substituted phenyl and aralkyl moieties such as benzyl, methylbenzyl and phenylethyl. Other organic moieties include substituted hydrocarbon moieties, such as halo (e.g., chloro-, fluoro- and bromo-substituted hydrocarbons) and oxy- (e.g., alkoxy substituted hydrocarbons) substituted hydrocarbon moieties. Preferred organic moieties are alkyl, alkenyl and alkynyl moieties having from 1 to about 8 carbon atoms, and halo-substituted derivatives thereof. Particularly preferred are alkyl moieties of 4 to 6 carbon atoms.

In the cyanoacrylate monomer of formula (III), R^3 is preferably an alkyl group having 1–10 carbon atoms or a group having the formula $-AOR^9$, wherein A is a divalent straight or branched chain alkylene or oxyalkylene moiety having 2–8 carbon atoms, and R^9 is a straight or branched alkyl moiety having 1–8 carbon atoms.

Examples of groups represented by the formula $-AOR^9$ include 1-methoxy-2-propyl, 2-butoxy ethyl, isopropoxy ethyl, 2-methoxy ethyl, and 2-ethoxy ethyl.

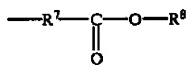
The preferred alpha-cyanoacrylate monomers used in this invention are 2-octyl cyanoacrylate, dodecyl cyanoacrylate, 2-ethylhexyl cyanoacrylate, butyl cyanoacrylate, methyl cyanoacrylate, 3-methoxybutyl cyanoacrylate, 2-butoxyethyl cyanoacrylate, 2-isopropoxyethyl cyanoacrylate, or 1-methoxy-2-propyl cyanoacrylate.

The alpha-cyanoacrylates of formula (III) can be prepared according to methods known in the art. Reference is made, for example, to U.S. Pat. Nos. 2,721,858 and 3,254,111, each of which is hereby incorporated by reference herein. For example, the alpha cyanoacrylates can be prepared by reacting an alkyl cyanoacetate with formaldehyde in a non-aqueous organic solvent and in the presence of a basic catalyst, followed by pyrolysis of the anhydrous intermediate polymer in the presence of a polymerization inhibitor. The alpha-cyanoacrylate monomers prepared with low moisture content and essentially free of impurities are preferred for biomedical use.

The alpha-cyanoacrylates of formula (III) wherein R^3 is a group having the formula $-R^4-O-R^5-O-R^6$ can be prepared according to the method disclosed in U.S. Pat. No. 4,364,876 to Kimura et al., which is hereby incorporated by reference herein. In the Kimura et al. method, the alpha-

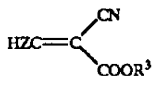
cyanoacrylates are prepared by producing a cyanoacetate by esterifying cyanoacetic acid with an alcohol or by transesterifying an alkyl cyanoacetate and an alcohol; condensing the cyanoacetate and formaldehyde or para-formaldehyde in the presence of a catalyst at a molar ratio of 0.5–1.5:1, preferably 0.8–1.2:1, to obtain a condensate; depolymerizing the condensation reaction mixture either directly or after removal of the condensation catalyst to yield crude cyanoacrylate; and distilling the crude cyanoacrylate to form a high purity cyanoacrylate.

The alpha-cyanoacrylates of formula (III) wherein R^3 is a group having the formula



can be prepared according to the procedure described in U.S. Pat. No. 3,995,641 to Kronenthal et al., which is hereby incorporated by reference herein. In the Kronenthal et al. method, such alpha-cyanoacrylate monomers are prepared by reacting an alkyl ester of an alpha-cyanoacrylic acid with a cyclic 1,3-diene to form a Diels-Alder adduct which is then subjected to alkaline hydrolysis followed by acidification to form the corresponding alpha-cyanoacrylic acid adduct. The alpha-cyanoacrylic acid adduct is preferably esterified by an alkyl bromoacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct. Alternatively, the alpha-cyanoacrylic acid adduct may be converted to the alpha-cyanoacrylyl halide adduct by reaction with thionyl chloride. The alpha-cyanoacrylyl halide adduct is then reacted with an alkyl hydroxyacetate or a methyl substituted alkyl hydroxyacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct or carbalkoxy alkyl alpha-cyanoacrylate adduct, respectively. The cyclic 1,3-diene blocking group is finally removed and the carbalkoxy methyl alpha-cyanoacrylate adduct or the carbalkoxy alkyl alpha-cyanoacrylate adduct is converted into the corresponding carbalkoxy alkyl alpha-cyanoacrylate by heating the adduct in the presence of a slight deficit of maleic anhydride.

Examples of monomers of formula (III) include cyanopentadienoates and alpha-cyanoacrylates of the formula:



(IV)

wherein Z is —CH═CH_2 and R^3 is as defined above. The monomers of formula (IV) wherein R^3 is an alkyl group of 1–10 carbon atoms, i.e., the 2-cyanopenta-2,4-dienoic acid esters, can be prepared by reacting an appropriate 2-cyanoacetate with acrolein in the presence of a catalyst such as zinc chloride. This method of preparing 2-cyanopenta-2,4-dienoic acid esters is disclosed, for example, in U.S. Pat. No. 3,554,990, which is hereby incorporated by reference herein.

Preferred monomers are alkyl alpha-cyanoacrylates and more preferably octyl alpha-cyanoacrylates, especially 2-octyl alpha-cyanoacrylate. Monomers utilized in the present application should be very pure and contain few impurities (e.g., surgical grade).

Compositions of the present invention may include at least one plasticizing agent that imparts flexibility to the polymerized monomer formed on the wound or incision. The plasticizing agent preferably contains little or no moisture and should not significantly affect the polymerization of the monomer.

Other compositions are exemplified by U.S. Pat. Nos. 5,259,835 and 5,328,687 and U.S. patent applications Ser. Nos. 08/609,921, 08/714,288, 08/909,845, 08/755,007, 08/920,876, and 08/488,411, all incorporated by reference herein in their entirety.

Examples of suitable plasticizers include acetyl tributyl citrate, dimethyl sebacate, triethyl phosphate, tri(2-ethylhexyl)phosphate, tri(p-cresyl)phosphate, glyceryl triacetate, glyceryl tributyrate, diethyl sebacate, dioctyl adipate, isopropyl myristate, butyl stearate, lauric acid, trioctyl trimellitate, dioctyl glutarate and mixtures thereof. Preferred plasticizers are tributyl citrate and acetyl tributyl citrate. In embodiments, suitable plasticizers include polymeric plasticizers, such as polyethylene glycol (PEG) esters and capped PEG esters or ethers, polyester glutarates and polyester adipates.

Compositions of the present invention may also include at least one acidic stabilizing agent that inhibits polymerization. Such stabilizing agents may also include mixtures of anionic stabilizing agents and radical stabilizing agents.

Examples of suitable anionic stabilizing agents include, but are not limited to, sultones (e.g., α-chloro-α-hydroxy-o-toluenesulfonic acid-γ-sultone), sulfur dioxide, sulfuric acid, sulfonic acid, sulfurous acid, lactone, boron trifluoride, organic acids, alkyl sulfate, alkyl sulfite, 3-sulfolene, alkylsulfone, alkyl sulfoxide, mercaptan, and alkyl sulfide and mixtures thereof. Preferable anionic stabilizing agents are acidic stabilizing agents of organic acids such as acetic acid or phosphoric acid. In embodiments, the amount of sulfur dioxide stabilizer is less than 100 ppm, preferably 5–75 ppm, and more preferably from about 20–50 ppm. The amount of sultone and/or trifluoracetic acid is about 500–3000 ppm.

Examples of suitable radical stabilizing agents include hydroquinone, hydroquinone monomethyl ether, catechol, pyrogallol, benzoquinone, 2-hydroxybenzoquinone, p-methoxy phenol, t-butyl catechol, butylated hydroxy anisole, butylated hydroxy toluene, and t-butyl hydroquinone.

Suitable acidic stabilizing agents include those having aqueous pK_a ionization constants ranging from −12 to 7, preferably from about −3.5 to about 6, and more preferably from about 2 to about 5.5. For example, suitable acidic stabilizing agents include: hydrogen sulfide (pK_a 7.0), carbonic acid (pK_a 6.4), triacetylmethane (pK_a 5.9), acetic acid (pK_a 4.8), benzoic acid (pK_a 4.2), 2,4-dinitrophenol (pK_a 4.0), formic acid (pK_a 3.7), nitrous acid (pK_a 3.3), hydrofluoric acid (pK_a 3.2), chloroacetic acid (pK_a 2.9), phosphoric acid (pK_a 2.2), dichloroacetic acid (pK_a 1.3), trichloroacetic acid (pK_a 0.7), 2,4,6-trinitrophenol (picric acid) (pK_a 0.3), trifluoroacetic acid (pK_a 0.2), sulfuric acid (pK_a _3.0), and mixtures thereof.

When adding the above-mentioned acidic stabilizing agents to the adhesive composition, the addition of plasticizing agents in amounts ranging from about 0.5 wt. % to about 16 wt. %, preferably from about 3 wt. % to about 9 wt. %, and more preferably from about 5 wt. % to about 7 wt. % provides increased film strength (e.g., toughness) of the polymerized monomer over polymerized monomers having amounts of plasticizing agents and acidic stabilizing agents outside of the above ranges.

The concentration of the acidic stabilizing agents utilized may vary depending on the strength of the acid. For example, when using acetic acid, a concentration of 80–200

ppm (wt/wt), preferably 90–180 ppm (wt/wt), and more preferably 100–150 ppm (wt/wt) may be utilized. When using a stronger acid such as phosphoric acid, a concentration range of 20–80 ppm (wt/wt), preferably, 30–70 ppm (wt/wt) and more preferably 40–60 ppm (wt/wt) may be utilized. In embodiments, the amount of trifluoroacetic acid is about 100 to 3000 ppm, preferably 500–1500 ppm. In other embodiments, the amount of phosphoric acid is about 10–200 ppm, preferably about 50–150 ppm, and more preferably about 75–125 ppm.

Other compositions are exemplified by U.S. Pat. Nos. 5,624,669, 5,582,834, 5,575,997, 5,514,371, 5,514,372, 5,259,835 and 5,328,687, incorporated by reference herein in their entirety. The compositions of the present invention may also include at least one biocompatible agent effective to reduce active formaldehyde concentration levels produced during in vivo biodegradation of the polymer (also referred to herein as "formaldehyde concentration reducing agents"). Preferably, this component is a formaldehyde scavenger compound. Examples of formaldehyde scavenger compounds useful in this invention include sulfites; bisulfites; mixtures of sulfites and bisulfites; ammonium sulfite salts; amines; amides; imides; nitriles; carbamates; alcohols; mercaptans; proteins; mixtures of amines, amides, and proteins; active methylene compounds such as cyclic ketones and compounds having a b-dicarbonyl group; and heterocyclic ring compounds free of a carbonyl group and containing an NH group, with the ring made up of nitrogen or carbon atoms, the ring being unsaturated or, when fused to a phenyl group, being unsaturated or saturated, and the NH group being bonded to a carbon or a nitrogen atom, which atom is directly bonded by a double bond to another carbon or nitrogen atom.

Bisulfites and sulfites useful as the formaldehyde scavenger compound in this invention include alkali metal salts such as lithium, sodium and potassium salts, and ammonium salts, for example, sodium bisulfite, potassium bisulfite, lithium bisulfite, ammonium bisulfite, sodium sulfite, potassium sulfite, lithium sulfite, ammonium sulfite, and the like.

Examples of amines useful in this invention include the aliphatic and aromatic amines such as, for example, aniline, benzidine, aminopyrimidine, toluene-diamine, triethylenediamine, diphenylamine, diaminodiphenylamine, hydrazines and hydrazide.

Suitable proteins include collagen, gelatin, casein, soybean protein, vegetable protein, keratin and glue. The preferred protein for use in this invention is casein.

Suitable amides for use in this invention include urea, cyanamide, acrylamide, benzamide, and acetamide. Urea is a preferred amide.

Suitable alcohols include phenols, 1,4-butanediol, d-sorbitol, and polyvinyl alcohol.

Examples of suitable compounds having a b-dicarbonyl group include malonic acid, acetylacetone, ethylacetone, acetate, malonamide, diethylmalonate or another malonic ester.

Preferred cyclic ketones for use in this invention include cyclohexanone or cyclopentanone.

Examples of suitable heterocyclic compounds for use as the formaldehyde scavenger in this invention are disclosed, for example, in U.S. Pat. No. 4,127,382 (Perry) which is hereby incorporated by reference herein. Such heterocyclic compounds include, for example, benzimidazole, 5-methyl benzimidazole, 2-methylbenzimidazole, indole, pyrrole, 1,2,4-triazole, indoline, benzotriazole, indoline, and the like.

A preferred formaldehyde scavenger for use in this invention is sodium bisulfite.

In practicing the present invention, the formaldehyde concentration reducing agent, e.g., formaldehyde scavenger compound, is added in an effective amount to the cyanoacrylate. The "effective amount" is that amount sufficient to reduce the amount of formaldehyde generated during subsequent in vivo biodegradation of the polymerized cyanoacrylate. This amount will depend on the type of active formaldehyde concentration reducing agent, and can be readily determined without undue experimentation by those skilled in the art.

The formaldehyde concentration reducing agent may be used in this invention in either free form or in microencapsulated form. Other compositions are exemplified by U.S. patent application Ser. No. 08/714,288, incorporated by reference herein in their entirety.

When microencapsulated, the formaldehyde concentration reducing agent is released from the microcapsule continuously over a period of time during the in vivo biodegradation of the cyanoacrylate polymer.

For purposes of this invention, the microencapsulated form of the formaldehyde concentration reducing agent is preferred because this embodiment prevents or substantially reduces polymerization of the cyanoacrylate monomer by the formaldehyde concentration reducing agent, which increases shelf-life and facilitates handling of the monomer composition during use.

Microencapsulation of the formaldehyde scavenger can be achieved by many known microencapsulation techniques. For example, microencapsulation can be carried out by dissolving a coating polymer in a volatile solvent, e.g., methylene chloride, to a polymer concentration of about 6% by weight; adding a formaldehyde scavenger compound in particulate form to the coating polymer/solvent solution under agitation to yield a scavenger concentration of 18% by weight; slowly adding a surfactant-containing mineral oil solution to the polymer solution under rapid agitation; allowing the volatile solvent to evaporate under agitation; removing the agitator; separating the solids from the mineral oil; and washing and drying the microparticles. The size of the microparticles will range from about 0.001 to about 1000 microns.

The coating polymer for microencapsulating the formaldehyde concentration reducing agent should be polymers which undergo in vivo bioerosion, preferably at rates similar to or greater than the cyanoacrylate polymer formed by the monomer, and should have low inherent moisture content. Such "bioerosion" can occur as a result of the physical or chemical breakdown of the encapsulating material, for example, by the encapsulating material passing from solid to solute in the presence of body fluids, or by biodegradation of the encapsulating material by agents present in the body.

Examples of coating materials which can be used to microencapsulate the formaldehyde concentration reducing agent include polyesters, such as polyglycolic acid, polylactic acid, poly-1,4-dioxa-2-one, polyoxaltes, polycarbonates, copolymers of polyglycolic acid and polylactic acid, polycaprolactone, poly-b-hydroxybutyrate, copolymers of epsilon-caprolactone and delta-valerolactone, copolymers of epsilon-caprolactone and DL-dilactide, and polyester hydrogels; polyvinylpyrrolidone; polyamides; gelatin; albumin; proteins; collagen; poly(orthoesters); poly(anhydrides); poly(alkyl-2-cyanoacrylates); poly(dihydropyrans); poly(acetals); poly(phosphazenes); poly(urethanes); poly(dioxinones); cellulose; and starches.

Examples of the surfactant which can be added to the mineral oil include those commercially available under the designations Triton x-100, Tween 20 and Tween 80.

The composition of this invention may further contain one or more adjuvant substances, such as thickening agents, medicaments, or the like, to improve the medical utility of the monomer for particular medical applications.

Suitable thickeners include, for example, polycyanoacrylates, polylactic acid, polyglycolic acid, lactic-glycolic acid copolymers, polycaprolactone, lactic acid-caprolactone copolymers, poly-3-hydroxybutyric acid, polyorthoesters, polyalkyl acrylates, copolymers of alkylacrylate and vinyl acetate, polyalkyl methacrylates, and copolymers of alkyl methacrylates and butadiene. Examples of alkyl methylacrylates and acrylates are poly(2-ethylhexyl methacrylate) and poly(2-ethylhexyl acrylate), also poly (butylmethacrylate) and poly(butylacrylate), also copolymers of various acrylate and methacrylate monomers, such as poly(butyl methacrylate-co-methylacrylate).

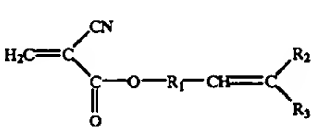
To improve the cohesive strength of adhesives formed from the compositions of this invention, difunctional monomeric cross-linking agents may be added to the monomer compositions of this invention. Such crosslinking agents are known. Reference is made, for example, to U.S. Pat. No. 3,940,362 to Overhults, which is hereby incorporated by reference herein. Examples of suitable crosslinking agents include alkyl bis(2-cyanoacrylates), triallyl isocyanurates, alkylene diacrylates, alkylene dimethacrylates, trimethylol propane triacrylate, and alkyl bis(2-cyanoacrylates). A catalytic amount of an amine activated free radical initiator may be added to initiate polymerization of the cyanoacrylate monomer/crosslinking agent blend.

The compositions of this invention may further contain fibrous reinforcement and colorants, i.e., dyes and pigments. Examples of suitable fibrous reinforcement include PGA microfibrils, collagen microfibrils, cellulosic microfibrils, and olefinic microfibrils. Examples of suitable colorants include 1-hydroxy-4-[4-methylphenyl-amino]-9,10 anthracenedione (D+C violet No. 2); disodium salt of 6-hydroxy-5-[(4-sulfophenyl)axo]-2-naphthalene-sulfonic acid (FD+C Yellow No. 6); 9 -(o-carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthen-3-one, disodium salt, monohydrate (FD+C Red No. 3); 2-(1,3-dihydro-3-oxo-5-sulfo-2H-indol-2-ylidene)-2,3-dihydro-3-oxo-1H-indole-5-sulfonic acid disodium salt (FD+C Blue No. 2); and [phthalocyaninato (2-)] copper.

Depending on the particular requirements of the user, the adhesive compositions of this invention can be applied by known means such as with a swab, glass stirring rod, sterile brush or medicine dropper. However, in many situations a spray dispensing package is preferred in which the adhesive composition is in solution with a compatible anhydrous propellant. Other modes of application are exemplified in U.S. patent application Ser. No. 08/488,411, incorporated by reference herein in its entirety.

What is claimed is:

1. An adhesive composition with improved properties of chemical durability, flexibility and elasticity of resulting polymers and copolymers, comprising a compound of the following formula (I):



(I)

wherein R_1 is selected from the group consisting of alkyl having at least 2 carbon atoms, alkoxy, anhydride, ether, ester, and amide, wherein R_2 and R_3 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, hydroxy, alkenyl, ester, carboxylic acid, ether and electron withdrawing groups, and

wherein R_1 may also optionally be omitted or be an alkyl having 1 carbon atom when R_2 and R_3 are not both hydrogen.

2. The adhesive composition according to claim 1, wherein said electron withdrawing groups are selected from the group consisting of halogens, amides, cyanos, esters, acids and ethers.

3. The adhesive composition according to claim 1, wherein R_1 is an alkyl having from about 2 to 8 carbon atoms.

4. The adhesive composition according to claim 1, wherein R_2 and R_3 are hydrogen.

5. The adhesive composition according to claim 1, wherein R_2 and R_3 are alkyls having from 1 to 3 carbon atoms.

6. The adhesive composition according to claim 1, further comprising an initiator.

7. The adhesive composition according to claim 6, wherein said initiator is selected from the group consisting of benzalkonium chloride, stannous octoate and sodium tetradecyl sulfate.

8. The adhesive composition according to claim 1, further comprising a radical initiator.

9. The adhesive composition according to claim 8, wherein said radical initiator is selected from the group consisting of di-t-butyl peroxide, azobisisobutyronitrile and benzoylperoxide.

10. A method of joining together surfaces, comprising:

(a) holding together at least two surfaces to form abutted surfaces, and

(b) applying across said abutted surfaces an adhesive composition according to claim 1.

11. An adhesive composition comprising a homopolymer of the compound of claim 1.

12. An adhesive composition comprising a copolymer of the compound of claim 1 and a 1,1-disubstituted ethylene monomer.

13. The adhesive composition according to claim 12, wherein said ethylene monomer is n-butyl cyanoacrylate or 2-octyl cyanoacrylate.

14. The adhesive composition according to claim 1, wherein crosslinking occurs through the vinyl terminated ester group.

15. The adhesive composition according to claim 1, further comprising an ultraviolet initiator.

16. A method of treatment comprising using the adhesive composition of claim 1 in a biomedical application selected from the group consisting of drug delivery, burn treatment, setting fractured bone structures, retarding blood flow from wounds, aiding repair and regrowth of living tissue and apposing surgically incised or traumatically lacerated internal or external tissues.

17. The adhesive composition according to claim 1, further comprising at least one acidic stabilizing agent.

18. The adhesive composition according to claim 17, further comprising at least one radical stabilizing agent.

19. The adhesive composition according to claim 18, further comprising at least one plasticizing agent.

* * * * *

Exhibit 6

Recent advances in bone grafting

Daniel E. Lehman, MD, and Bruce T. Rougraff, MD

Despite many recent studies to evaluate alternative options with which to treat bone defects, autograft remains the gold standard. Many products have recently been developed that are available as promising alternatives to autograft; they do not have the morbidity associated with autograft but neither do they have equal effectiveness in addressing bone defects. Inasmuch as no one material is apparently sufficient to replace autograft bone, there is the possibility that a combination of materials is necessary to allow for adequate replacement and new bone formation.

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The traditional method of treating bone defects has been through the use of autograft bone. Because of donor site morbidity and graft strength, however, other bone grafting techniques have been developed. These techniques include vascularized autografts, freeze-dried allograft chips, segmental allografts, demineralized allograft matrix, and synthetic hone substitutes.

Autogenous bone grafts

Autograft may be either cancellous, cortical, or a combination of both and vascularized or nonvascularized. Autogenous bone graft provides osteogenesis, *ie,* living bone-producing cells. Additionally, autograft allows for osteoconduction, a passive process by which the bone structure serves as a scaffold upon which new bone is formed. Autograft also results in osteoinduction. Through osteoinduction, mesenchymal cells surrounding the graft are recruited hy various biologic signals to differentiate into osteoblasts.

Both cortical and cancellous autografts share the properties described here. Cortical autografts are also ahle to provide structural support while hone formation is occurring. tJnfortunately, as integration of the graft is occuring, there is a weakening of the cortical graft due to resorption within the graft. This weakness results in the graft being at risk for fracture prior to complete incorporation. Nonvascularized autografts are ideal for small defects of the metadiaphysis or for acute trauma or nonunions. They likewise work well for large metaphyseal or epiphyseal defects. Large diaphyseal bone defects require structural grafts and hardware support for most rapid reconstitution. Defects greater than 8 cm typically are too large for nonvascularized autogenous structural grafts.

Vascularized autogenous bone graft

In the 1970s, vascularized bone grafting was established as a reliable technique. This technique allows for the transfer of bone with its blood supply intact. Vascularized bone graft is thought to have less resorption of hone, fewer fatigue fractures, more rapid union of hone, and rapid hypertrophy of hone. This makes it a good choice for the reconstruction of larger diaphyseal defects. Common donor sites of vascularized bone include the fibula, ribs, and iliac crest.

Han *et al.* [1] have reviewed 160 vascularized bone transfers for the reconstruction of tumors, nonunions, congenital anomalies, and infection. They found a primary union rate of 61% An additional 20% of patients obtained union after

secondary procedures. Patients who underwent reconstruction following tumor resection, for congenital anomalies, and to treat noninfected nonunions had a higher rate of union than patients who had an infected nonunion. The authors also found that the use of stable internal fixation resulted in a higher rate of primary incorporation than the use of external fixation.

One of the complications of free vascularized transfer, venous occlusion, was evaluated in a rabbit model by Janowski*et al.* [2]. In this study, the rate of graft incorporation was most rapid in the vascularized group, intermediate in the group in which the venous pedicle was occluded, and slowest in the cortical autograft group. The authors concluded that obstruction of the venous outflow does not necessarily eliminate the ability of the graft to consolidate.

Allografts

One of the limitations of autograft reconstruction is that an ample amount of autogeneic bone may not be available, particularly in the reconstruction of tumors. This limitation has stimulated the use of allografts in the reconstruction of bone defects. Allograft bone does not impart osteogenesis but does allow for osteoconduction and to some extent osteoinduction. Problems associated with the use of allograft tissue include viral transmission as well as antigenic incompatihility. Processing of allograft tissue may decrease antigenicity and may be done by freezing the bone or by first removing the water from the bond as is done in freeze-drying. Vigorous tissue testing for viral contamination is routinely done by bone procurement centers, but viral transmission is still possible.

Mankin *et al.* [3] in 199Z, reported on their experience with allografts primarily for reconstruction following tumor resection with large segmental loss. They reported a success rate of 80%. Complications included fracture in 19%, nonunion in 14%, and infection in 10%. A longer term problem has been the development of osteoarthritis in patients who have undergone osteoarticular grafting. This problem was noted in 17% of patients who had undergone an osteoarticular reconstruction.

Smaller studies have shown a similar rate of complications following allograft reconstruction. Brien*et at.* [4], in 17 patients, found a high rate of complications including deep infection in three patients and a superficial infection in a fourth patient, nonunion in two patients, and amputations in three patients (with two of these due to infection).

Vander Griend [5] recently reported the influence of internal fixation on the healing of larger allografts. In his review of 120 allografts, he found no difference in the rate of union in comparing the use of an intramedullary nail with use of a plate. He did find that the plate fixation was associated with a higher rate of fracture. He also determined that in the majority of patients in whom bone-host junctions did not heal, there was inadequacy of the stability of the internal fixation.

Allograft consolidation was also evaluated by Aranguren *et al.* [6'] in 83 allografts. In their study, the mean time to consolidation for metaphyseal junctions was 6.5 months, with a mean time to consolidation in the diaphysis of 16 months. For the diaphyseal osteotomy group, 19% of the osteotomies required an additional autogenous bone graft to achieve union. Fractures were noted in eight of the 83 allografts. Factors associated with a significant decrease in consolidation of the diaphyseal osteotomies included chemotherapy, radiation, and older patient age.

Wang and Shih [7], in 1993, found that the supplementation of autograft bone at the allograft-host junction was able to shorten the union time from 15 months to 8 months. In their small study, they were not able to show an adverse effect related to chemotherapy and bone healing. Mnaymneh*et a/.* [8] evaluated 96 distal femoral osteoarticular allografts with an average follow-up of 4.4 years. In this series, complication rates were similar to those reported by Mankin*ef a/.* [3]. Arthritis had developed in 10% of patients. Of note was the fact that both infection and nonunion rates were significantly higher in the patients who received chemotherapy.

Zatsepin and Burdygin [9] reviewed a large series of osteoarticular allografts about the knee with longterm follow-up. In this series of 156 grafts, 16 patients developed an infection. Fracture of the graft was found in 35 patients. Although the development of a graft-host nonunion was not noted to be a problem, most of the 11 fractures that were found during the first 5 years following implantation were located at the graft-host junction. Degenerative arthritis of the knee was noted in most patients, especially those with distal femoral allografts.

Aho *et al.* [10] reviewed 37 allografts, most of which were osteoarticular grafts. Degenerative changes were noted in 20 of the Z9 osteoarticular grafts. Infection developed in 11% of grafts but did not necessitate the removal of the graft. Fractures were noted in 27% of patients; however, no patient had a nonunion of the graft-host junction.

Alternative bone graft choices

Because of the limited availability of autograft and the numerous complications experienced with allografts, many other alternatives for bone defect reconstruction are currently being explored. These alternatives include the use of demineralized bone, bone-stimulating proteins, and synthetic bone substitutes.

Demineralized bone

Demineralized bone is obtained by taking cortical allograft bone and removing the surface lipids and dehydrating the bone with ethanol and ethyl ether. The bone is then processed with hydrochloric acid. This process removes acidsoluble proteins in the bone, leaving behind protein, bone growth factors, and collagen. This bone can then either be implanted in strips or processed into smaller particles. The demineralized bone is both osteoconductive and osteoinductive.

Reddi *et al.* [11] have outlined the steps that follow implantation of the demineralized bone. Briefly, a hematoma forms, which leads to an inflammatory phase associated with the migration of polymorphonuclear lymphocytes. Fibroblastlike mesenchymal cells then come into contact with the matrix. The demineralized bone then stimulates DNA synthesis, which leads to the transformation of the mesenchymal cells into chondrocytes by the 5th day after implantation. The chondroblasts then form a cartilage matrix, that is subsequently calcified, leading to the development of new bone.

Although the demineralized bone matrix does not have structural rigidity, it has been shown in an animal model to compare favorably with autograft with regard to both mechanical strength and rate of union [1Z]. Yang*et al.* [13] also evaluated demineralized bone matrix in a rabbit model. They found that demineralized bone matrix healed at a rate between autograft, which healed with the most success, and freeze-dried bone, which had the least success at incorporation. Although the combination of a freeze-dried fibular strut with demineralized bone matrix at the host-graft junctions achieved good success in terms of incorporating the demineralized bone matrix into the host bone, this did not improve the incorporation of the allograft strut. Kubler *ef a/.* [14] compared demineralized bone matrix with freeze-dried bone in a rat model. They found that the demineralized bone demonstrated chondrogenesis and osteogenesis in 50%of the animals whereas the freeze-dried bone did not induce new bone or cartilage formation. Hagen*et al.* [15] evaluated bone induction in a rat model using demineralized bone. In their study, the demineralized bone was found to induce bone formation. There was, however, a persistent rim of connective tissue that developed at the interface between the host and the demineralized bone graft. This rim was found to persist with time. Dupoirieux *et al.* [16] found that demineralized bone matrix resulted in the induction of bone formation in 90% of rats by 2 months after implantation. Becker *et al.*[17] found an absence of bone induction in athymic mice that received demineralized bone matrix implants.

Clinical studies of demineralized bone matrix have had mixed results. Tiedeman *et al.*[18] combined demineralized bone matrix with bone marrow to treat osseous defects in 39 patients. They were able to obtain a 77%success rate. Patients who had fracture nonunions were found to have a lower success rate. Demineralized bone matrix has also been used in periodontal reconstructions. In these situations, there have been mixed results with regard to incorporation of the demineralized bone matrix. Becker *et al.*. [19] compared the induction of bone formation using autologous bone with that of demineralized bone. They found that extraction sockets that were packed with autologous bone resulted in new bone formation whereas sockets packed with demineralized bone showed no evidence of new bone formation or of osteoclastic activity against the demineralized bone.

Bone morphogenic protein

Johnson *et al.* [2O] demonstrated benefit from combining bone morphogenic protein with autolyzed, antigenextracted, allogeneic bone in a study of 25 nonunions. Twenty-four of the *25* nonunions healed after the implantation of this composite graft. Sailer *et al.* [21] also demonstrated the effectiveness of bone morphogenic protein in enhancing the repair of cranial-facial defects. In a report on their experience with 145 patients, it was the authors' opinion that the addition of bone morphogenic protein significantly aided in the repair of these defects.

Weiss *et al.* [22] evaluated the effect of transforming growth factorp and basic fibroblast growth factor on osteogenesis in a rat model. In this study, which also used autograft cancellous bone, transforming growth factorp was found to enhance osteogenesis with limited angiogenesis whereas the basic fibroblast growth factor was found to enhance angiogenesis with little influence on osteogenesis. The authors suggested that future studies are required to evaluate the effect of synergistic activity of these growth factors on new bone formation.

Coralline hydroxyapatite

Coralline hydroxyapatite is available from Interpore International (Irvine, GA) and marketed as ProOsteon. It is created by taking sea coral and subjecting the coral to a hydrothermal exchange reaction. The size of the pore within the graft is dependent on the species of coral that is used. The effect of coralline pore size was evaluated by Kuhne *et al.* [23]. In this study, implants with a pore size of 200 p,m were compared with implants with an average pore size of 500 p,m. The coralline hydroxyapatite with a pore size of 500 p,m was found to have a significantly higher rate of osseous integration when compared with the smaller-pore-size material. C:oralline hydroxyapatite serves as a lattice for host bone to grow through (osteconductive). The material is very slowly (if at all) resorbed by the body. Goralline hydroxyapatite is approved for grafting acute metaphyseal fractures of long bones.

Collagraft is a synthetic bone graft substitute developed by Zimmer, Inc., and the Collagen Corp. It is approved by the t J.S. Food and Drug Administration for grafting in acute fractures treated with internal fixation and defects less than 30 cm-. Collagraft is a combined product of hydroxyapatite, tricalcium phosphate, and bovine fibrillar collagen. It is to be used with supplemental autogenous bone marrow.

Conclusions

Despite many recent studies evaluating alternative options for treating bone defects, autograft remains the gold standard. Many exciting products are now available as alternatives to autograft. 'I'hese products do not cause the morbidity associated with autograft but they have not been shown to have equal effectiveness in repairing bone defects. It appears that no single material may be sufficient to replace autograft bone. Perhaps a combination of materials is necessary to allow for adequate replacement and new bone formation.

References and recommended reading

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